Plants

The Potentials for Extracting Protein, Medicines, and Other Useful Chemicals

Workshop Proceedings

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Preface

The Workshop Proceeding, *Plants: The Potentials for Extracting Protein, Medicines, and Other Useful Chemicals,* was prepared in response to a request from the Senate Committee on Agriculture, Nutrition, and Forestry that OTA examine technological opportunities for commercially developing plant extracts. The proceeding describes some opportunities and constraints of commercially developing plant extracts, examples of some work being done in this field, and workshop participants' conclusions and recommendations concerning the Government's role in the area. Ten technical papers and four overview papers are included in the proceeding.

Developing new crops or plant products offers a wide range of potential benefits to the United States and developing countries. Crop diversification and new product development in the United States may substitute domestically produced goods for petroleum and other imports (including strategic and essential industrial materials); provide useful new consumer products; increase productive use of land resources, especially in marginal farming areas; generate employment in areas of underemployment or unemployment; and provide plant-derived biocides that cause little long-term ecological damage as alternatives to certain synthetic pesticides. In developing countries, new crops or new plant-derived products may help stimulate cottage industries, increase local and national self-sufficiency, and perhaps provide new export industries. This proceeding addresses these opportunities as well as constraints to and possible impacts of their development.

In regard to protein extraction from tobacco, the proceeding states that the risk involved in investment in this technology is perceived to be high, and a considerable concern exists that products would have limited marketability because of:

- the health concerns that some attach to tobacco, and
- the changed character of cigarettes and chewing tobacco made from protein-extracted tobacco may not satisfy consumers.

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I.

Overview of Subject/Issue

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Overview of Subject/Issue

Historically, plants have served humankind as sources of foods, medicines, oils, biocides, waxes, and other useful substances. However, it was not until the early 19th century that active compounds were isolated in a pure form from plants, and late in the 19th century that the chemical structures of natural plant compounds could be determined. A revolution in chemical technology has occurred in the last 50 years. New technologies have enabled the isolation, identification, and subsequent synthesis of biological compounds. Although some chemical compounds found in plants cannot be synthesized today because of technical or economic constraints, an increasing number of chemical compounds are being produced in the laboratory.

Despite these capabilities, renewed interest has developed in using naturally produced chemicals from plants—botanochemicals—as sources of new food proteins, medicines, biocides, and other materials. The rapid escalation of petroleum prices has encouraged Government and industry to consider plants as renewable sources of botanochemicals that could reduce the demand for petroleum resources. Similarly, concern for adequate food supplies, especially in less developed countries, has drawn attention to new technologies for extracting high-quality protein from tropical legumes for livestock feed and human consumption. Better understanding of the ecologically disruptive and persistent effects of some synthetic biocides has stimulated work on extracting biocidal compounds from plants—e.g., insecticides from the neem tree. Because plant-derived biocides are biodegradable, they rarely persist for long periods; their impact, although perhaps initially as disruptive to the ecosystem as a synthetic substance, is temporary.

While only a small proportion of all higher plants has undergone chemical testing, statistically the probability is high that many unscreened plants contain important substances for human use. The greatest reservoirs of unscreened plants, however, are in tropical regions, where changes in land use are leading to the permanent loss of some of these resources before they can be assessed. As a result of the disappearance of tropical species, there is a sense of urgency to increase screening efforts and investigate commercial potential of tropical plant chemicals.

The objective of the OTA exploratory workshop was to provide a basis for general discussion of opportunities, constraints, and potential impacts of new crop and new plant product development rather than to carry out a comprehensive investigation of potential commercial plant products. The subjects chosen for discussion, therefore, represent only a small sample of plant products with commercial potential. An effort was made to include examples of different types of products, including low cost/large demand and high cost/small demand products; products suitable for development both in the United States and in less developed countries; and plants that have had little previous commercial use—namely, arid/semiarid land plants and marine plants. In addition to papers on specific plant products, papers on the existing data bases on plant-derived drugs and on ecological characteristics of minor economic plant species were presented. Short summaries of each of the papers follow.

II.

Abstracts of Workshop Papers

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TOBACCO LEAF PROTEIN

Pilot-scale technology that extracts high-quality protein from young tobacco leaves has been developed. Soluble proteins extracted from tobacco plants might be added to foods as nutritional supplements or for functional properties (e.g., gelling, thickening). Although not fully tested, they might have a specialized medicinal use as a pure protein source for kidney patients. Insoluble proteins might be suitable as a supplemental livestock feed. The leaf material left after protein extraction might be used in the manufacture of safer cigarettes with lower concentrations of toxic substances.

Several important constraints to the development of this technology make its future uncertain. Because a stigma is attached to tobacco by a large segment of society, there is a strong likelihood that food products developed from tobacco would not be readily accepted by the general public. Tobacco would face strong competition from alternate sources of protein. Before this technology could be economically viable, the residual deproteinized tobacco would have to be marketed successfully for the manufacture of smoking products, such as cigarettes. Significant flavor changes and associated characteristics of the deproteinized tobacco may not satisfy consumer tastes. Lastly, expanding the technology from the pilot scale to commercial scale will require the solution to certain technical and economic problems.

PROTEIN FROM TROPICAL PLANTS

The leaves of some 500 tropical plants have been screened by the U.S. Department of Agriculture (USDA) as potential sources of high-protein animal and human foods. Leaf protein fractionation for livestock feed is based on the principle that nitrogen-fixing plants contain higher levels of protein than ruminant animals can use, and nonruminants can assimilate only a portion of the total plant protein but cannot consume the volume of leaves necessary to meet their protein needs. The high-protein content of these plants allows partial removal of protein for nonruminant use and subsequent use of the remainder of the plant and its protein by ruminants. An appropriate combination of animals for the dual-use of leaf protein would be hogs and dairy cattle.

The plants with the greatest potential for commercial LPC (leaf protein concentrate) production are herbaceous nitrogen-fixers. Tropical grasses are naturally too low in nitrogen to be adequate sources of LPC. Fertilization with nitrogen increases the protein content, but the expense of commercial fertilizer is too great to make LPC production economical. Many tropical tree leaves contain toxic and antinutritional compounds which limit their use as livestock feed. Processing of the leaves might rid them of these harmful compounds, but the additional cost and technology requirements to do so might be prohibitive.

Work on alfalfa in the United States, Europe, and Japan has demonstrated the potential for dual-use of plant protein and has provided techniques and machinery that may be adapted to tropical plants. Although extraction and use of leaf protein in tropical regions seems promising, especially as livestock feed, a number of areas need additional research, including extraction methods, energy needs, acceptance of products, year-round vegetation supply, plant protein content, plant substances that adversely affect animal and human nutrition, environmental impacts, and cost. The feasibility of human use of LPC in tropical countries has been contested on grounds of health and practicality. Especially on small farms, protein probably can be better supplied through direct consumption of high-protein vegetables such as collards, mustard greens, amaranthus, and the winged bean.

ENDOD IN COMBATING SCHISTOSOMIASIS

The berries of endod (*Phytolacca dodecandra*), the Ethiopian soapberry plant, after being dried, ground, and mixed with water, are used in Ethiopia and elsewhere as a detergent for washing clothes in rivers and streams. More importantly, within hours the solution can kill snails that carry schistosomiasis, a debilitating disease affecting an estimated 200 million to 300 million people and potentially infecting as many as 400 million others in many tropical and subtropical countries. The rapidly spreading disease poses a threat to large-scale irrigated agriculture and hydroelectric power development schemes in the tropics, many of which receive partial support from U.S. development assistance institutions.

A 5-year field study of endod's effectiveness against schistosomiasis in Ethiopia showed that after streams were treated with endod, the overall prevalence of the disease in 17,000 local people dropped from an initial 63 to 34 percent. In children of ages 1 to 6, the incidence of disease dropped from 50 to 7 percent. This and other tests indicate that endod, in combination with other drugs to treat already infected people, holds promise for controlling schistosomiasis and other snail-borne diseases.

MILKWEED: A POTENTIAL NEW CROP FOR THE WESTERN UNITED STATES

Arid/semiarid-land plants already are valuable sources of commercial products, including candelilla wax, jojoba oil, gum arabic, tragacanth gum, and natural rubber from guayule. However, many other arid and semiarid land plants represent largely untapped sources of chemicals for industrial feedstocks and other products. For example, pilot-scale research indicates that the showy milkweed (*Asclepias dodecandra*) contains many commercially exploitable chemicals. As with many plants, significantly higher value is obtained by fractionation of the plant material into component parts, any one of which alone would not economically justify milkweed as a crop. The development of milkweed as a commercial crop is contingent on solving certain agronomic and processing problems and on the development of markets for milkweed products.

Dryland agriculture using milkweed and other potential arid/semiarid crops could be ecologically and economically beneficial, especially in marginal areas now cultivated with traditional food and fiber crops. For example, milkweed might be preferable to existing crops in the western Great Plains where crop irrigation is causing overuse of the ground water. Developing new arid and semiarid crops also might expand agriculture to areas that now cannot be cultivated with existing crops. Before development of new crops is promoted on arid/semiarid lands generally considered to be ecologically fragile, cropping systems and other agronomic techniques must be available to minimize ecological disruption.

INSECT REPELLANTS, ATTRACTANTS, AND TOXICANTS FROM ARID/SEMIARID LAND PLANTS

Many arid- and semiarid-land plants have been identified as potential commercial sources of natural insect attractants, repellants, and toxicants. Because these plant-derived chemicals are biodegradable, they might prove to be preferred alternatives to synthetic chemicals that persist in the environment long after application. Arid/semiarid plants may be potential new crops on lands that are marginal or unproductive for traditional food and fiber crops.

USDA screening has identified seven plants as particularly promising commercial sources of natural insecticides, insect repellants, or attractants. These are sweetflag (*Acorus calamus*), big sagebrush (*Artemisia tridentata*), neem (*Azadirachta indica*), Heliopsis (*Heliopsis longipes*), mamey apple (*Mamea americana*), sweet basil (*Ocimum basilicum*), and Mexican marigold (*Tagetes minuta*). Most of these plants have been used in other countries for various purposes on a local level but have not been developed on a large commercial scale.

Of the seven plants discussed, the neem tree seems to have the greatest potential as a commercial crop. Although all parts of the tree repel insects, the seeds are outstanding repellants and feeding deterrents for a wide range of household and agricultural pests. The rest of the tree—timber, bark, and leaves—has a variety of economic uses for construction and medicinal and hygenic applications. The tree grows well where many other plants present an erosion hazard or are unproductive, as in hot, dry climates and on shallow, stony, or sandy soils. Neem could be encouraged as a crop to further local economic development, especially in arid zone countries. Currently, there are neem plantations in India and in African, Latin American, and Caribbean countries. USDA has a program to develop neem as a commercial crop in Puerto Rico and the U.S. Virgin Islands.

COMMERCIAL PRODUCTS FROM MARINE PLANTS

Marine plants have evolved unique biochemical processes and structures in adapting to their chemical, physical, and biological environments. Although marine plant biochemistry is a relatively new field, research done to date reveals that marine algae represent potential sources of pharmaceuticals, agricultural chemicals, foods and food products, industrial chemical feedstocks, and other useful products. Despite this potential, little commercial development of marine plant products has occurred in the United States, with the exception of agar, carageenan, alginate, and beta-carotene for the food industry; chemicals for biomedical research; and glycerol for a variety of consumer products.

The success of tapping the rich potential of marine plants will depend on greater support of basic research in marine biochemistry, genetics, nutrition, reproduction, and mass culturing techniques. However, little Government funding for commercial development of marine extracts is available, and private sector activities in the field are limited, especially in pharmaceutical development. To ensure that basic research is translated into commercial application, a close link must be developed among Government, universities, and industry. The Sea Grant Program, funded by the Department of Commerce, provides such a link and demonstrates the effectiveness of such collaboration.

ANTICANCER DRUGS FROM THE MADAGASCAR PERIWINKLE

The isolation, purification, and subsequent marketing of alkaloids from the Madagascar periwinkle (*Catharanthus roseus*) in the late 1950's and early 1960's instigated a resurgence of interest in plants as possible sources of anticancer drugs. Among the many periwinkle alkaloids showing anticancer activity, leurocristine* and vincaleukoblastine** have reached the marketplace and are among the most effective cancer chemotherapy treatments available today. Vincristine, called a "miracle drug" because it was on the market less than 4 years after its discovery, shows a 50-percent-complete response rate in children with lymphocytic leukemia when administered alone and a 90-percent-complete response rate in combination therapy.

In addition to providing a valuable medicine for cancer patients, the periwinkle alkaloids have been very profitable to Ely Lilly, the pharmaceutical firm that developed the drugs. Despite the financial benefits resulting from research on the Madagascar periwinkle, Eli Lilly has shut down its plant screening program. It was the last U.S. pharmaceutical firm to have such a program. The U.S. Government has followed suit; the National Cancer Institute's program to test plants for antitumor activity was discontinued in 1981. Now that these two research programs have been discontinued, there are no major initiatives in the United States to search for anticancer drugs from plants.

The potential of plants as sources of new antitumor drugs has not been fully explored; the chemical compositions of only a small portion of the Earth's higher plant species have been chemically investigated. Despite the problems and high costs of developing new drugs, the success of the work on *Catharanthus* alkaloids illustrates that new drugs can be developed from plant resources, and at a profit. The reasons behind the current lack of research on antitumor drugs and the respective roles of the private and public sectors in such research should be examined.

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*Known generically as vincristine.

**Known generically as vinblastine.

STRATEGIC AND ESSENTIAL INDUSTRIAL MATERIALS FROM PLANTS

The U.S. dependence on imports of essential industrial materials (including "stragetic" materials essential to national defense) and petroleum for industrial feedstocks and fuel could be reduced by domestic production of plants yielding these substances or their substitutes. In 1979, the United States imported an estimated $16.5 billion worth of petroleum for industrial feedstock and $6.5 billion worth of agriculturally produced industrial materials, of which some $3.5 billion was for newsprint and $1 billion was for chemicals extracted from plants. Domestic production of a portion of these materials could decrease the Nation's dependence on finite petroleum resources and increase U.S. dependence on agriculturally produced renewable resources.

Producing these materials in the United States could benefit farmers and manufacturers through crop and product diversification. The Nation could benefit from import substitution, reduced dependence on other countries for supplies of strategic and essential materials, and elimination of the need to stockpile strategic materials. Large-scale domestic production of industrial crops would require reallocation of large areas of land from other uses to these crops. Assessments of land availability and the ecologic and social impacts of altering land use should be considered. In addition, a great deal of research is needed on plant breeding and agronomy of potential industrial crops (e.g., guayule, crambe, jojoba, lesquerella, meadowfoam). Clearly, domestic production of industrial crops would be economically beneficial, but several social, economic, ecological, political, and foreign policy implications should be carefully examined.

INFORMATION USEFUL TO PLANT-DERIVED DRUG PROGRAMS

Plants play a major role in medicine. Plant-derived drugs represent approximately 25 percent of total prescriptions dispensed. The retail value in 1980 of U.S. prescription drugs containing active compounds from higher plants* is estimated to be at least $8 billion and over-the-counter drugs at some $1 billion. Because synthesis of almost all of the 50 pure-plant compounds used in prescriptions is not technically or economicaly feasible now, most of these compounds still are extracted from plants.

Despite the proven value of plant compounds as pharmaceutical ingredients, natural product development virtually has stopped and little work is being done on tissue-culturing and genetic engineering for production of plant-derived drugs. Drug development is relying increasingly on synthesis of new compounds. The reasons for the disinterest in plant-derived drugs may be lack of an assured plant supply, feelings that patent protection on natural products is insecure, or a sense that natural products research is unprofitable.

Plant drug development entails many steps, including plant selection and collection, bioassay procedures, isolation and identification of biologically active plant compounds, and clinical evaluation and marketing. Any shortcuts to systematize plant selection for screening and select appropriate bioassay procedures would decrease research time and expense and increase the chances of discovering marketable chemicals. Ten automated data bases that provide data on plant sciences, agriculture, and the chemistry and pharmacology of natural products can be used as screening aids for plant extracts work. One of these data bases, NAPRALERT, consisting of computerized files of research findings and published folklore information relevant to plant-derived drugs, can be extremely valuable to research on plant-derived drugs.

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*Higher plants are those such as conifers and flowering plants, which possess a well-developed conducting system. Plants such as mosses, fungi, and algae are not part of this group.

USDA'S DATA BASE ON MINOR ECONOMIC PLANTS

Large numbers of plant species exist with commercial potential that remain undeveloped as crops. There is an overwhelming number of climatic, ecological, and anthropological variables associated with these plants. Since 1971, the USDA Economic Botany Laboratory has been developing a computerized information system on minor economic plant species. The system's files include information on agronomy, agroforestry, ecology, ethnomedicine, nutrition, pathology, and uses of several hundred plants. There is also a climate file with data for over 20,000 locations worldwide. A wide variety of questions can be answered by linking these files through a computer. For example, the system can help match new crops with environments in which they would be most successful, identify potential multipurpose crops for certain locations, determine the yield and nutritional value of a particular plant under given ecologic and agronomic conditions, help determine the potential spread of an introduced weed or pest, and identify sources of plants or specific germ plasm useful for crop improvement. These files are now off-line because of lack of funding. If maintained on-line and developed further, the system could be a valuable tool for new crop- and plant-product development.

III.

Summary and Discussion of Each Workshop Paper

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TOBACCO LEAF PROTEIN

The concept of using leaf protein as a food is not new. Over the last 60 years, scientists from several countries have researched the extractability of proteins from leaves and preparation of leaf protein concentrate (LPC). The greatest impetus for leaf protein research came in the early 1940's when Norman Pirie of England examined the potential of producing LPC as a source of protein for human consumption to alleviate wartime food shortages. After World War II the interest in leaf proteins for human use waned because their green color and slightly grassy taste hindered consumer acceptance of them as human foods. Since that time, the Pirie process for leaf protein extraction has been modified for commercial production of LPC for livestock feed. Recently, a new technique has been developed and tested at the pilot-plant stage that can extract a high-quality, purified protein from immature tobacco plants. It has been proposed that tobacco be used as a dual- or multi-product crop for proteins and smoking and chewing tobacco.

The extraction process yields six products. They are:

Crystalline Fraction 1 Protein

Fraction 1 protein is a water-soluble, tasteless, and odorless white powder. It is nutritious; when fed to rats, crystalline Fraction 1 protein exhibited a higher protein efficiency ratio (PER) than casein, the common standard for comparing the nutritional quality of proteins. Because it is tasteless and odorless, Fraction 1 protein can be added to foods to improve their protein content and quality without changing their taste or smell. This product can be added to foods for its albumin-like functional properties such as heat set and gelling. It has been suggested that if crystalline Fraction 1 is washed free of sodium and potassium, it might be useful for kidney patients as a source of high-quality protein, although this has not been substantiated by research.

Fraction 2 Protein

This product also is water-soluble and nutritious and might be used as a protein supplement for food products such as cereals. Its functional properties are not so desirable as those of Fraction 1 protein, however.

Green Sludge

Green sludge consists of water-insoluble proteins and starch. It possibly could be marketed as a feed for poultry and other nonruminant animals. Green sludge can be converted by solvent extraction to a material similar to soybean meal in properties and amino acid composition.

Green Residue

This product represents the fibrous material left after protein extraction. The solids are composed of more than 50 percent cellulose and hemicellulose and about 13 percent protein. It is similar to alfalfa hay in nutritional value. The green residue can be converted through organic solvent extraction to white fibers suitable for cigarette manufacturing. The resultant deproteinized cigarettes would be lower in tar and nicotine than commercial cigarettes today.

Pigments and Other Bio-Organic Compounds

Organic solvent extraction of the green residue and green sludge produces pigments and other organic compounds. Carotenoids can be separated out and possibly marketed as poultry feed supplements.

Low-Molecular Weight Compounds

This product, composed of water-soluble sugars, amino acids, vitamins, salts, and other compounds, might be used as a fermentation liquor after it is concentrated by evaporation.

The extraction procedure for tobacco protein is fairly simple. First, the aboveground portions of the tobacco plants are crushed. The liquid is pressed out, leaving behind the solids (green residue). The green juice is heated rapidly to 125° F (52° C) then quickly cooled to room temperature, causing green particulate matter (green sludge) to settle out of the now brown liquid. The brown juice is pumped to a storage tank where within 6 to 10 hours Fraction 1 protein crystallizes out of solution. The crystals are collected and washed. The remaining liquid is acidified, causing Fraction 2 proteins to precipitate out of solution. They, too, are collected and washed.

The process has the following advantages: providing a high-quality protein from a plant already grown on a total of 2.5 million hectares over a wide geographical range, and providing a smoking product that is lower in the constituents believed to be health hazards. Although the results of pilot-scale research seem promising, several technical, economic, social, and environmental problems would have to be solved before tobacco protein extraction could be viable on a commercial scale.

This procedure was developed by Leaf Protein, Inc. (LPI), a small venture capital corporation. To investigate the potential of this process on a commercial scale, LPI formed a joint venture with the North Carolina Farm Bureau Federation. The Federation, together with General Foods Corp., helped finance a pilot plant in the tobacco growing region of North Carolina, a small plant able to process about a ton of fresh plants every 9 to 10 hours. The plant was operated first in August 1980. Each experiment required a minimum of 600 lbs of fresh plants. Climatic and technical problems were encountered, and it was not until July 1982 that the pilot plant was consistently able to produce Fraction 1 protein of high purity. Although the pilot-scale operations appeared promising, at the end of the tobacco growing season the research facility was closed and the equipment was sent to the University of Florida which is using it experimentally to produce pig feed. The research was discontinued because of lack of industry interest in investing in commercial scale-up of the LPI process. This lack of interest was not caused by predicted scaling-up problems but by fears that the products would have limited marketability because of the social stigma attached to tobacco and the changed character of cigarettes and chewing tobacco would not gain consumer acceptance. The risk involved in investment was perceived to be too high.

Consumer attitude is perhaps the most serious deterrent to using tobacco as a source for protein. Given tobacco's negative image in the eyes of many American consumers, the appeal for foods containing tobacco leaf protein could be questionable. Tobacco protein would have to compete with the already abundant sources of protein in the United States—ranging from vegetable oilseed proteins to animal proteins—which are well-established and probably more readily acceptable to the public. The potential retail value of the extracted protein alone would not economically justify growing tobacco since all three proteins together account for only about 20 percent of the total estimated value of the finished products from tobacco. As much as 55 percent of the crop's estimated value would come from sale of the fibrous portion for cigarette manufacture. Unless the deproteinized fiber is acceptable to manufacturers **and** consumers, the process would not be profitable. No commercial firm has been willing to invest in commercial scaling-up of the LPI system. Whether the changed character of a cigarette would appeal to consumer taste is in question but will be a major factor in the economic success of tobacco protein extraction.

There are many technical constraints facing the LPI process, both at the agronomic and the processing level. The time at which the tobacco is harvested is critical because the leaf protein is surprisingly variable on a daily basis. Because the proteins and other leaf constituents deteriorate rapidly after harvesting, the harvested material must be processed almost immediately. At the processing level, the leaf pulp is difficult to work with when using conventional conveying machinery because it is viscous and is corrosive to metal. Another problem which is not so apparent at the pilot level as on the commercial level is disposal of wastes. Since about 90 percent of the plant material is water, handling and disposal of large amounts of fluid must be arranged. The brown juice left after extraction of the proteins and fiber has a high biological oxygen demand (BOD) so would be a source of pollution if released unaltered into an aquatic system. Evaporation processes to condense the liquids, however, are expensive. Solvent recovery is another problem. Because they are expensive, a certain proportion of the solvents used in processing green residue and green sludge must be recovered. This may be a problem encountered with commercial scale-up.

The environmental impacts of tobacco as a crop should be examined. Tobacco needs large inputs of energy, biocides (insecticides, herbicides, fungicides, nematicides), and fertilizers for cultivation. When grown in the conventional manner, tobacco is "hard on the soil." It readily extracts soil nutrients, particularly nitrogen, so unless large amounts of fertilizer are applied to tobacco fields, the crops over time will tend to decrease soil fertility. When grown for protein extraction, tobacco plants could be harvested four times per growing season. This faster rotation probably would lead to even faster nutrient depletion and would require greater fertilizer inputs than even conventional tobacco crops. Cultivation of tobacco, an annual planted at relatively wide spacing, presents an erosion hazard. The denser spacing used for protein tobacco compared with conventional tobacco might help reduce erosion rates. However, more frequent harvests, repeatedly exposing the soil to wind and rainfall, probably would increase erosion.

Conventional tobacco production requires large inputs of biocides. Pesticide inputs may decrease because the "cosmetic" appearance required of the cigarette tobacco leaf is not necessary for protein extraction. Seedlings either would be raised in seedbeds that have been fumigated to kill micro-organisms and then transplanted in the field or would be raised directly in newly cleared land. The latter obviously is not desirable or possible in many places. The need for herbicide application would be greater if tobacco were grown for protein extraction because repeated harvests provide increased opportunity for weed encroachment. It seems that growing tobacco for protein extraction would be equally, if not more, ecologically disruptive than conventional tobacco, a crop widely recognized as a resource-demanding crop.

A great deal more economic information is needed to assess the commercial viability of the process. No processing costs at the pilot level or projected commercial processing costs are available. In addition, the ability of the products to enter the marketplace must be assessed. The products would have to be able to compete on the market with alternative products in price, availability, ease of use, and consumer taste preference (with products for human consumption). For example, Fraction 1 protein would have to compete with egg albumin as a functional food additive and the bio-organic compounds from the green residence and green sludge with alfalfa as a source of carotenoids for poultry feed. Both egg-whites and alfalfa are well-established in these markets and tobacco might have difficulty attracting a portion of these markets away from them. Most important, the deproteinized tobacco fibers would have to be able to compete with mature, cured tobacco leaves. Not only would a different taste have to be acceptable to the consumer, but the processor would have to be willing to make processing changes for the new product. An important factor in market entrance is the amount of product available. If only limited quantities of a product in a large-volume market (e.g., fibers for tobacco or for livestock feed) are available, industry may be unwilling to go to the trouble and expense of using small and/or intermittent amounts of the products.

Although the LPI process appears promising at the pilot-level scale, a great number of technical, ecological, social, and economic barriers stand in the way of commercial feasibility. The cost of taking this process from the pilot-plant scale to commerical production scale could be high. Although the pilot-plant operation was supported by private capital, the private sector is showing reluctance to work with a tobacco-related product. Despite potential advantages of the products, financial backing for further research on agronomics, extraction, and product testing and marketing has not been forthcoming. It seems that tobacco processors are not interested in altering an already profitable manufacturing system to incorporate processing of tobacco proteins of uncertain marketability, and that the food industry is unwilling to invest in a crop carrying such a social stigma. In addition, tobacco proteins have not undergone mandatory Food and Drug Administration (FDA) testing on animals to assess their safety for human consumption. Until this happens food processors may be leery of the possible presence of toxic compounds in the proteins.

There is some evidence that the protein extraction process might be used successfully on soybeans, clover, alfalfa, tomato, spinach, and other crops which are less ecologically disruptive and more socially acceptable. These plants would face many of the same problems with research and commercial scale-up that tobacco faces, but could be more acceptable to producers and consumers. Perhaps further research should investigate these alternative crops for LPI processing.

PROTEIN FROM TROPICAL PLANTS

At the present growth rate, world population will double within the next 30 to 40 years. This population increase will be most rapid in the less developed countries of the humid lowland Tropics, where annual increase in food production remains low. LPC extracted from tropical plants is being investigated as a possible source of protein. LPC is prepared from alfalfa on a large commercial scale in Europe and the United States. Because alfalfa has not been grown successfully in the humid Tropics, suitable tropical replacements are needed for leaf protein extraction.

Leaf protein fractionation is based on the principle that nitrogen-fixing plants contain higher levels of protein than can be used by ruminant animals and that nonruminants, able to assimilate only a portion of total plant protein, cannot consume the volume of leaves necessary to meet their protein needs. The high protein content of these plants allows for partial removal of protein for nonruminant use and subsequent use of the remainder of the plant by ruminants.

USDA's Tropical Agriculture Research Station in Mayaguez, Puerto Rico, has tested at least 500 introductions of tropical plants as possible sources of LPC. Desirable characteristics of plants as sources of leaf protein concentrate include high protein content, high dry-matter content, readily extractable protein from freshly cut plants, good regrowth potential, ability to fix nitrogen, erect growth for easy mechanical harvesting, nontoxicity, and low concentration of antinutritional substances.

The extraction procedure used was a relatively simple process in which the liquid pressed out of the leaves was subjected to successively higher temperatures, thus causing the proteins to precipitate out of solution. At 55° C, a green coagulum formed and was separated by centrifugation, washed several times, and spread in thin layers on glass plates to dry. The supernatant from the centrifugation was heated carefully to 64° C. The white curd coagulum that formed was separated by centrifugation, washed with acetone, and dried in a rotary evaporator. The liquid was heated further to 82° C. After cooling, a light tan precipitate formed and was processed in the same way as the 64° C fraction.

The spontaneous coagulation of protein in the juice extracted from some plants (subsequently called Type I plants), including cassava (*Manihot esculenta*), leucaena (*Leucaena leucocephala*), and many other tree legumes, was observed during the survey of tropical plants. Another group of plants (Type II) yielded a green protein coagulum after the extracted green plant juice was heated to 55° C and yielded a very small quantity of a light tan precipitate at 82° C. This first was observed with leaf protein extract of sorghum-sudan grass hybrids and other grasses. Careful heat fractionation of aqueous leaf extracts of other plants (Type III) yielded three distinct protein fractions: a green coagulum at 55° C, a copious white protein precipitate at 64° C, and a small amount of light tan precipitate at 82° C. These are the most promising plants for leaf protein extraction; species selected for further study were chosen from this group. A final group (Type IV) includes plants in which the proteins in the aqueous extracts do not precipitate either spontaneously or after heat treatment.

Leaf protein concentrates subsequently were prepared from seven Type III plants (*Vigna unguiculata, Clitoria ternatea, Desmodium distortum, Psophocarpus tetragonolobus, Macroptilium lathyroides, Phaseolus calcaratus, Brassica napus*) and leucaena and cassava, both Type I plants. The protein quality of the LPC extracted from these plants was evaluated using rats. The tropical legumes cowpea (*Vigna unguiculate*), *Desmodium distortum*, rice bean (*Phaseolus calcaratus*), and winged bean (*Psophocarpus tetragonolobus*) gave excellent results, comparable to those obtainable from alfalfa LPC. The LPC from these plants had amino acid contents similar to each other and to reported values for alfalfa LPC and soybean meal. The tests supported the suspicion that the spontaneously precipitated protein concentrate from Type I plants would have less nutritional value; rats fed LPC from cassava and leucaena grew poorly. USDA investigations indicated that with current methods, good quality leaf protein concentrates for nonruminants could not be prepared from many of the leguminous tree leaves because the presence of phenolic substances negatively affects the nutritional value of the extracted proteins. The leaves of some of these species, however, could be used as feed for ruminants.

Investigations of tropical grasses as sources for leaf protein extraction showed them to be low in extractable protein. Nitrogen fertilizer could be applied to fields to increase the protein content in grasses, but the increased value probably would not offset the cost of the fertilizer. Tropical grasses were considered poor sources of LPC because they have higher production and processing costs and lower quality and quantity of extractionable proteins.

The following conclusions were drawn from this relatively short investigation of possible tropical plant sources for leaf protein extraction:

- Some tropical plants are sources of LPC that are equivalent to alfalfa LPC in yield, extractability, and nutritional quality.
- A single crop in the Tropics cannot be used for year-round production; a pattern of different plants has to be formulated for rainy and dry seasons.
- Cassava, leucaena, other tropical trees, and tropical grasses seem to be unpromising as potential sources of LPC.
- The type and number of protein fractions obtained by heat fractionation can be used as a rapid preliminary method to screen plants for protein extraction potential.

Machinery has been developed in England and the United States for LPC processing. Some are used for large-scale commercial LPC operations in Europe and the United States, and others have been used to assess its viability for on-farm and village-level LPC production. Research on village-level LPC production has been carried out in India, Pakistan, and Sri Lanka. Work in Aurangabad, India, is the most relevant to practical application of the LPC production systems on the village level. Establishment of a commercially viable, locally operated LPC production unit at a village farm was attempted. The green protein concentrate from alfalfa was used as a milk replacement for calves (thus making the cow milk available for human consumption), as poultry feed, and as human food. The pressed crop was fed immediately to cows. The cost of equipment and a dairy unit of five to six cows was assessed at $4,450, which is prohibitively expensive for a small-farm operator but probably affordable for village cooperatives. Concurrent research in India on LPC production concluded that on a nutritional basis, leaf protein would be much less expensive than most protein from grain legumes consumed in the area and that a LPC-containing product made for human consumption could provide half the daily protein requirements of a child at a price affordable to the majority of Indian poor ($0.025 to $0.03 per day).

On-farm leaf protein fractionation has been researched in Britain, Australia, and the United States. The on-farm system is that after harvesting, the crop is processed to produce pressed forage for ruminants and a juice with soluble proteins for nonruminants. Processing takes place on a farm and at least one of the products is used at the production site. The ideal situation would be a combined dairy and hog farm where the crop is grown and extraction products used onsite, thus reducing transportation expenses, storage costs, and spoilage. Research at the University of Wisconsin at Madison has concentrated on development of a weather-independent, on-farm forage-harvesting system using a protein fractionation process. After harvesting, the main produce is pressed forage that can be preserved directly as silage. Field losses from harvesting and baling are reduced and a higher percentage of the protein content can be retained in pressed residue than in sundried hays. Research results indicate that ruminants respond to being fed pressed residue as they do nonfractionated plants. The juice extracted from the plant material could be fed directly to hogs to minimize storage and preservation expenses. The proteins in the juice degrade rapidly and the carbohydrates ferment within a day, so the processing must be geared to the feeding time of the animals. Proteins could be isolated from the juice by fermentation, but the product is not acceptable yet to hogs.

Commercial LPC production was initiated in 1967 at the USDA Western Regional Research Center in Berkeley, Calif. A highly mechanized process, the Pro-Xan process, was developed for obtaining LPC from alfalfa. The first commercial application of this process took place in France in association with a commercial alfalfa dehydrators plant. (Dehydration is carried out immediately after harvesting to avoid losses from haymaking and ensiling and to produce a product higher in protein content than hay or silage.) Leaf protein concentrate from alfalfa now is prepared on a large commercial scale in Europe and the United States for livestock feed. There are plans to open a plant in New Zealand, and two pilot plants have been set up in Japan.

Attempts to process LPC to obtain an acceptable good-grade product have been unsuccessful. Green LPC from the 55° C fraction can be produced economically, but its green color, grassy flavor, and low solubility have prevented acceptance by consumers and food producers. Purifying this protein concentrate by solvent extraction is technically feasible but costly and only partially effective. The white protein fractions separated at 64° and 82° C are nutritious but are practically insoluble. If soluble, they would be of greater use to the food industry. Producing a water-soluble, bland-tasting white protein using various filtration techniques including diafiltration, ultrafiltration, and gel filtration has been attempted. Although gel filtration seems to be the most effective system, it is very expensive. Another method has been developed that produces a pure, water-soluble protein at a lower price than gel filtration. This is a crystallization process used to extract Fraction 1 protein from tobacco.* Although this process seems to be technically feasible at the pilot-plant level, its economic feasibility has not been proven and has encountered constraints to commercial scale-up.

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*See paper by Wildman in the appendix.

Use of LPC technology in developing countries is most promising as applied to medium-sized production systems such as cooperatives, organized communities, and large farms. On-farm production of LPC is too expensive and labor-intensive to be feasible for most farmers who own or lease small plots of agricultural land. The system is probably most adaptable to cooperative farming operations, such as a combined dairy-hog operation. Onsite use of the products offers many advantages including lower transportation and storage costs, reduced waste because leaf production can be coordinated with demand for LPC and pressed fodder, and ability to use excess pressed juice for irrigation water.

Large-scale LPC production might be possible in developing countries if incorporated into an integrated production system, such as an operation combining dairy or beef cattle with hogs or poultry. The high degree of coordination and planning of such an enterprise probably would restrict it to public ownership or to capital- and management-intensive private firms, such as beef exporters. While this would benefit foreign exchange earnings, it would fail to provide an inexpensive, efficient protein source for those in developing countries who need it most.

Screening of tropical plants for extractable protein has produced several good candidates for LPC production in tropical and subtropical countries. Processing machinery has been developed for alfalfa LPC production, but it might be adapted for use on tropical plants to meet developing country needs. Before LPC production using tropical plants is feasible, however, comprehensive studies should be conducted on agronomics of plants chosen for protein extraction, economic feasibility, farmers' acceptance of LPC extraction and use, and production technologies. A variety of agricultural, economic, and social factors and impacts must also be considered.

ENDOD IN COMBATING SCHISTOSOMIASIS

Rural people in Ethiopia and certain other countries traditionally have washed their clothes with a detergent solution made from dried and ground endod berries. Endod (*Phytolacca dodecandra*), the soapberry plant, is a shrub that is closely related to the American pokeweed plant. In 1964, researchers studying the distribution of disease-carrying snails in streams found large numbers of dead snails immediately downstream from people washing clothes using endod as a detergent. Subsequent phytochemical studies indicated that endod contains effective biocidal compounds. Endod is being studied as a potential molluscicide for use against snails that carry schistosomiasis.

Schistosomiasis is a debilitating snail-borne disease common throughout the Tropics and subtropics. It is one of the most serious and rapidly spreading parasitic diseases of humankind, affecting an estimated 200 million to 300 million people and potentially infecting an additional 400 million. The disease is spread when uninfected people work and bathe in the same water as infected people. New shallow-water habitats for snails, the intermediate hosts, have been created by irrigation, hydroelectric power, and other water-related projects, many of which have been funded by international agencies.

No single method to control schistosomiasis effectively has been found. Ideally the most effective treatment for the disease is site-specific and repeated molluscicide applications combined with mass treatment of all infected people, improved environmental sanitation, and health education. However, no safe, effective, and affordable drug suitable for mass treatment has been found, and available molluscicides are inadequate or expensive. Environmental sanitation and health education are long-range measures. For now the most practical and effective method to control schistosomiasis is through a combination of selective treatment of infected individuals and control of new transmission by killing the host snails at each proven site of infection.

Although several chemical molluscicides have been used within the last few decades to control schistosomiasis and other snail-borne diseases (e.g., copper sulphate, Frescon, sodium pentachlorophenate, Yurimin), several of them are no longer produced either because they are ineffective or cannot be marketed. The only molluscicide recommended by the World Health Organization is Bayluscide, an expensive chemical used only in a few developing countries with the help of external financial assistance. The lack of a market as a result of developing countries' limited foreign exchange has discouraged the private sector from developing other molluscicides. The discovery of endod and the lack of adequate and affordable chemical molluscicides have stimulated the testing of plants as potential molluscicides. Croton (*Croton tiglium, C. macrostachys*), ambrosia (*Ambrosia maratima*), and jatropha (*Jatropha curcas*) show some promising molluscicidal activity, but a great deal more work must be done to evaluate their potential as commercial molluscicides. As recognized by a workshop on plant molluscicides convened by the United Nations Development Programme, World Bank, and World Health Organization in January 1983, endod seems to be the most promising plant molluscicide evaluated to date. Whereas several other chemical molluscicides are unstable in intense sunlight or under different water pHs and concentrations of organic or inorganic matter in the water, endod remains stable in sunlight and under a wide range of water conditions. It is a potent molluscicide, killing snails within hours. Tests showed endod to have no mutagenic properties, indicating that widespread use of it as a molluscicide might not pose a safety hazard to humans.

A 5-year pilot study investigating the effect of endod on schistosomiasis was carried out in northern Ethiopia between 1969 and 1974. Systematic application of locally collected endod berries over the 5 years reduced the prevalence of schistosomiasis in children aged 1 to 6 from 50 to 7 percent, and in the entire population (17,000) from 63 to 34 percent. The incidence of disease in an untreated nearby village was almost constant over the course of the study, indicating that the reduction in the treated village was as a result of endod applications. The cost of the treatment amounted to only US $0.10 per person per year. A critical element in the success of this control study was local political support and community participation. The local political officials and municipal council were involved in the planning and execution of the study, and the council provided finances, manpower, and facilities.

In addition to its value as a molluscicide, the endod berry may have commercial potential as a detergent; an insecticide for the control of mosquitoes, the black fly that carries river blindness, and other water-breeding insects; a fungicide against certain human skin diseases; a spermaticide or an abortifacient. Endod berries have been used in Ethiopia and many other tropical countries for centuries to control an aquatic leach that is a major pest of livestock. The berries are also effective against snails that spread fascioliasis, a serious cattle and sheep disease.

Most chemical studies done on endod to date have focused on saponins, the biocidal compounds in the berries. Saponins account for only 25 percent of the dry weight of endod berries, and the berries in turn represent only a small proportion of the total plant biomass. The berries, leaves, stems, and roots could be potential sources of other useful products including pectins, thickening agents, starches, sugars, animal feed, and fuels. As research on endod progresses, these and other uses for the byproducts might be developed. Endod is a potential multipurpose crop that could provide products for local use or support local industries.

The active chemical in endod berries has been isolated, identified, and named Lemmatoxin. Three extraction procedures have been developed, two of which are based on solvent extraction and the third on fermentation. The fermentation method is simple; berries are ground, soaked in water, and left in a warm place to ferment by means of the yeast cells normally found on endod berries. This is perhaps the most practical extraction method for developing countries to use. Processing equipment is affordable, it can be supplied and operated locally, and no extraction solvents have to be imported. The fermentation extract can be applied in a variety of ways. It can be dusted on the surface of the water as a powder, sprayed on the water as an emulsion, or compressed into briquettes to allow for slow release of the active chemical.

If high-potency endod varieties could be grown locally, the dried and ground berries could be applied directly to rivers, streams, and irrigation channels. This would avoid the processing costs involved in preparing an extract. A study carried out between 1976 and 1981 tested 65 different strains of endod and chose three on the basis of molluscicidal potency, berry yields, and resistance to insect pests and drought. These three strains subsequently were used in cloning experiments using tissue culture. Plantlets developed through mass propagation have been distributed to Brazil and three African countries for field trials. Additional research is using tissue-culturing for in vitro biosynthesis of the active molluscicidal principle.

Although research on chemistry, extraction application, and toxicity of endod has progressed rapidly since 1964, a great deal more toxicological, agronomic, and economic research is necessary before large-scale application of endod for control of schistosomiasis and other snail-borne diseases could be possible. Toxicity studies on sheep and dogs showed that while intravenous injection of endod can be fatal, oral intake of small to moderate amounts can be tolerated by animals and large amounts induce vomiting. This emetic property acts to protect people and animals from possible overdoses. Endod berries, leaves, and roots have been taken orally for centuries in several African countries for various medical purposes, including birth control and ridding the body of internal parasites. Had endod shown negative effects, it probably would have been discarded long ago. Mutagenic tests on endod berries carried out in vitro have been negative. However, more comprehensive mutagenic and toxicity tests should be carried out on a variety of different animal species to provide more complete evidence of endod's safety.

Because endod has never been grown commercially on a large scale, it will have to be subjected to a range of agronomic studies. Agronomic research on endod during the last decade has concentrated on selection and breeding of plants for good growth and berry productivity and potency. Some studies have recently been carried out in Ethiopia on its plant ecology and susceptibility to pests, particularly to a stem-boring fly that kills young shoots. Data have also been collected on plant nutrition, germination, spacing, and irrigation. This preliminary work will have to be expanded; field trials are needed to determine both the agronomic needs of endod and the ecological effects of cultivating the plant, including impacts on soil, water availability, and pest outbreaks.

Although no comprehensive ecological studies to determine the effects of endod application on streams have been conducted, observations indicate that local animal populations are largely unaffected. Any localized effects of endod application are unlikely to be long-lasting because the active chemical biodegrades rapidly. Within 24 to 48 hours endod's potency declines. Extensive research is needed to provide comprehensive data on ecological impacts.

In summary, endod appears to be a promising potential as a molluscicide for controlling schistosomiasis. Research on endod, however, is still at an early stage. Before endod can be used as a molluscicide, far more research is needed on its toxicity, agronomy, ecology, economics, extraction, and application techniques, cost effectiveness compared to other molluscicides, and the distribution and marketing of berries or the extracted molluscicide. In addition, its potential as a multiproduct crop should be examined.

Endod could be a community-controlled solution in developing countries to the widespread problem of schistosomiasis. Because the plant can be grown locally and the biocidal compound extracted simply using a low-technology fermentation method, inexpensive local production of the molluscicide is possible. The alternative of importing expensive Bayluscide or another chemical molluscicide is not a viable option for most developing countries with limited foreign exchange. Endod could be cultivated and extracted either publicly or privately and then applied to infection sites by the community. The public sector would have to bear the startup research costs for such a community-based public health project, but financial assistance might be sought from development assistance agencies such as the U.S. Agency for International Development. Once started, a project could be sustained by local revenues and paid or volunteer community labor.

Endod use need not be restricted to schistosomiasis control in developing countries. Further research may develop endod's potential as a source of larvicides, insecticides, spermatocides, or other products. A similar community-based project based on the use of endod as a larvicide for the control of malaria perhaps is another future application. Endod might also be investigated as a biocide for pest control in the United States.

MILKWEED: A POTENTIAL NEW CROP FOR THE WESTERN UNITED STATES

Arid/semiarid-land plants in the United States represent relatively untapped sources of valuable oils, waxes, natural rubbers, insecticides, medicines, and important chemical feedstocks. These chemicals, produced by plants as defenses against predators, pests, and climatic stresses such as temperature extremes and drought, could be extracted to provide a variety of commercial products. Interest in arid/semiarid-land plants as sources of insect repellants, attractants, and toxicants;* fossil fuel substitutes; and chemical feedstocks** is growing. The showy milkweed (*Asclepias speciosa*), discussed in greater detail later, is an example of an arid/semiarid-land plant being investigated as a potential multipurpose crop for chemical feedstocks and fiber products. Arid and semiarid lands, often considered agriculturally unproductive in relation to traditional U.S. food and fiber crops, could become important for the production of a variety of commercial chemical extracts.

Despite the general lack of attention to the commercial potential of arid/semiarid-land plants, some of these plants already provide a variety of commercial products. Some arid/semiarid-land-plant extracts used in the United States are jojoba oil, gum arabic, tragacanth gum, candelilla wax, and natural rubber from guayule. Jojoba oil is a valuable lubricant able to withstand high temperatures. The first commercial harvest of cultivated jojoba plants in the Southwest United States occurred in 1982; until then only wild plants had been harvested. The market value of imports of gum arabic, used in the food industry for its functional properties, was about $8 million in 1982. Gum arabic is obtained from an *Acacia* species native to Africa and the Middle East, but a related species could be grown in the United States to supply an equivalent gum and provide savings in foreign exchange. Tragacanth gum is used in pharmaceuticals and cosmetics and as a thickening agent in some prepared foods. Although the plant could be grown in the United States, gum is imported from Iran. As a result of political instability in the area, imports recently have been erratic. The United States has had similar problems with procuring candelilla wax which is imported from Mexico. Imports dropped by over 50 percent between 1978 and 1982 as a result of harvesting problems. Guayule, a desert shrub that contains natural rubber, could be grown in the United States to provide a substitute for *Hevea* rubber imported from Southeast Asia. During World War II when the supply of imported rubber was cut off, guayule was produced in the Southwestern United States as an alternative source of natural rubber. Production was discontinued after the war when synthetic rubber became available and importation of natural rubber resumed. Interest in domestic production of guayule has again arisen with increasing demand for rubber and higher prices for hydrocarbons and petroleum-based industrial feedstocks. Semicommercial production is being carried out in the Southwest United States.*

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*See paper by Jacobson in the appendix.

**See paper by Tankersley and Wheaton in the appendix.

A major constraint to developing new arid/semiarid-land plants and plant products is lack of adequate field-screening procedures. The availability of good field-screening technologies could help identify promising species for research and locate good sources of germ plasm (e.g., for high oil content, high biomass productivity) for potential and existing crops. Chemical screening generally has been done in the laboratory by solvent extraction. Fairly recently, two laboratory techniques, wide-line nuclear magnetic resonance (NMR) and near-infrared reflectance (NIR), have been developed for more rapid screening. All three methods require that plants be brought in from the field for laboratory analysis. Solvent extraction must be done in the laboratory; NMR is not portable enough for field screening; and even though portable NIR units are available, plant material still has to be brought to the lab. Collecting, preparing, and documenting field samples are time-consuming activities, and because most of the material will be unpromising and therefore discarded, they are not cost effective. The plants yielding good laboratory results have to be relocated in the field, a task that is often difficult. It would be far more time- and cost-efficient if plants could be screened rapidly in the field and seeds or cuttings from the promising plants collected then. Lack of adequate field-screening techniques poses a serious deterrent to the search for potential new crops and plant products.

A plant should be screened for a range of chemical compounds to investigate its potential as a multiproduct crop. Once the plant material has been collected and transported to the processing site, additional costs for extracting more than one product may be relatively small but can add significantly to the total commercial value of the plant. Multiple-product development can justify the costs of growing, harvesting, and transporting the crop and extracting the chemicals. In addition, the development of many products helps buffer the market risk of the crop; if one product fails, the other products can help offset the economic loss.

Different techniques are used to extract particular chemicals. In general, polar solvents extract biologically active compounds and other reactive chemicals, including dyes, antioxidants, and adhesives. Nonpolar solvents yield compounds that are useful as lubricants, waxes, and elastomers. The water or acidic aqueous fraction may provide polysaccharides such as gum or pectin and some water-soluble protein. The residue from extraction is comprised of cellulose, hemicellulose, protein, and lignin (if present). This material may be burned as fuel, used as livestock feed, fermented to produce industrial chemicals, or the fiber may be removed and used for pulp, paper, or fabric.

Native Plants, Inc. (NPI) has been studying the showy milkweed (*Asclepias speciosa*) as part of a program to investigate plants as new sources of commercial chemicals. This species was chosen for study because it is distributed over a wide range of climates and soil types. It is an herbaceous perennial found throughout the Western United States, from the Mississippi River to the Pacific Ocean, and from central Alberta and Saskatchewan to central Oklahoma. Milkweed is a potential crop for areas of low rainfall. For example, *A. speciosa* can be grown easily in the western Great Plains, where overuse of the ground water stored in the Ogallala aquifer is requiring a shift from irrigated to dryland agriculture. Milkweed eventually may provide farmers with a substi-

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*See OTA background paper entitled *Water-Related Technologies for Sustainable Agriculture in Arid/Semiarid Lands: Selected Foreign Experience*, ch. V, for more information on guayule.

tute for irrigated crops or an alternative to other dryland crops (e.g., dryland wheat, grain, sunflowers, and sorghum) grown there. Most of NPI's work has been on milkweed's phytochemistry and extraction procedures. Although some research has been done on agronomy and crop storage, a great deal more is needed. In addition, the economic viability and ecological and social impacts of developing milkweed as a crop need to be examined carefully.

Fractionation of milkweed produces the following extracts with commercial potential: pigments, rubber, and triterpenoids from nonpolar solvent extraction; inositol and sucrose from polar extraction; and pectin from the acidic aqueous extract. The residue left after extraction consists of fibers that can be marketed for various commercial uses and fibrous material that is suitable for livestock feed. The material that can be used for feed represents 70 percent of the original plant biomass. It is equivalent to alfalfa in protein content and quality and in digestibility for sheep, but must undergo exhaustive solvent extraction or heat or acid treatment before it is rendered nontoxic.

Before commercialization of milkweed can be successful, much additional research on agronomy, harvesting, and crop storage is needed. Small test plots have been established by NPI in Utah, New Mexico, Texas, and Kansas. Attempts to establish stands elsewhere were unsuccessful and problems with controlling weeds and obtaining uniform stands were encountered. Developing effective methods of weed control, especially when the milkweed plants are still seedlings, is critical. Harvesting research indicates that plants can be harvested with standard farm equipment such as that used for alfalfa. Test plots gave yields of about 4.3 tonne/ha, but denser planting might be expected to yield between 6.7 and 9.0 tonne/ha. Storage tests indicated that although the nonpolar extractables remain stable, the polar extractables deteriorate over time when harvested material is stored. Covering the stored material alleviates the problem considerably. Storing the crop so that commercial processing could take place throughout the year would provide considerable financial savings in plant capacity.

Several environmental constraints must be considered before this crop is grown widely as a commercial crop. A major concern is that the arid and semiarid areas where milkweed cultivation has been tested are highly susceptible to erosion, especially by wind. The effectiveness of zero till, crop overseeding, sod culture, narrow stripcropping, and various other options should be evaluated. Another problem to be considered is loss of soil nutrients caused by removal of plant material. Nitrogen will have to be replaced by commercial fertilizer and possibly organic manure from cattle feedlots. Some pest problems should also be anticipated. Aphids are serious pests of milkweed and may become an economic liability in milkweed plantations. Pest control using natural predators and both natural and synthetic insecticides should be investigated. The danger of milkweed itself becoming a pest is an important consideration. Milkweed could cause considerable problems by spreading to neighboring fields planted in other crops. Wild populations of milkweed cause significant problems as weeds in some agricultural fields of Minnesota.

Major technical constraints will affect the profitability and competitiveness of milkweed compared with other crops. First, commercial extraction and purification of inositol and pectin (sweeteners), which together represent 58 to 73 percent of the total estimated value of milkweed products, are not yet commercially viable. Proto-commercial processing has uncovered other processing problems that must be resolved, and development of more efficient methods for detoxifying the residue for livestock feed is needed.

NPI calculated milkweed production costs using a 2-hectare research plot. The costs were found to be greater for milkweed than for dryland wheat or grain sorghum. Weed control accounted for more than half of total production costs. If weed control and harvesting techniques were improved, production costs could be reduced significantly. The milkweed seeds used in the research were collected from wild plants. Seed improvement through breeding, selection, and denser spacing of the plants could be expected to increase yields and improve the profitability of milkweed. The costs of erosion-control practices, not considered in the NPI analysis, should be factored in.

The total value of milkweed products ranges from $511 to $645 per tonne. These figures represent only the market value of the processed goods. Because no figures are available on processing costs to extract these materials from milkweed, market values indicate little about crop profitability. Processing costs may be considerable. For one thing, the costs of recovering extraction chemicals might be very high. As already mentioned, extraction and purification of inositol and pectin are difficult and expensive; economically viable techniques have not yet been developed. The other high-value products are triterpenoids, sucrose, fibers, and livestock feed. It is questionable how effectively sucrose and fibers from milkweed could move into the high-volume, well-established markets for these products. Livestock feed may prove to be competitive with other feed crops, especially on lands where these crops are unproductive such as areas of the western Great Plains. The potential of milkweed to substitute for fossil fuels as sources of hydrocarbons and chemical feedstocks can not be assessed from the information given. Before the economic feasibility of milkweed production can be predicted with any accuracy, more data on the costs of these products and the costs of producing alternatives from milkweed are needed. If milkweed products were to be moved into fossil-fuel related markets or other large-demand markets, large acreages of semiarid land might be converted to milkweed production. Ultimately, however, the competitiveness of milkweed as either a small-demand "specialty" crop or a large-demand crop is contingent on the marketability of the products. A great deal more marketing research must be done to assess milkweed's economic feasibility.

The scale of production is a vital consideration to the economic viability of milkweed. Large-scale production probably is needed to make it a profitable enterprise. Both the "specialty" or high-cost products (e.g., inositol, pectin) and the low-cost products (e.g., livestock feed, fiber) require large-scale production. Large amounts of milkweed are necessary to produce even small amounts of the more valuable products, and enough of the large-volume products must be available to capture a portion of their markets. If the economic viability of milkweed were dependent on inositol and pectin, care would have to be taken to avoid flooding the markets. A balance that could satisfy the demands of the low- and high-volume products would have to be reached. As will all new crops, scaling-up from pilot studies to commercial production would be the most difficult step and would be contingent on milkweed's attractiveness to investors.

If milkweed were to become commercially viable, it could provide many benefits. Although dryland wheat, grain, sorghum, and sunflowers are grown on the western Great Plains, the productivity of this area is not high in its contribution to total U.S. crop production. Substituting milkweed for these crops, therefore, would not reduce seriously the total production of traditional U.S. food and fiber crops. The western Great Plains is a cattle-feeding center. If milkweed were to replace some of the crops grown there for livestock feed, it could continue to supply feed necessary to support this industry. Milkweed could provide farmers with an alternative crop, thus freeing them from their dependence on commodity goods. Grain prices have remained stable, but operating costs have risen, so that the region's farming economy is severely depressed. If proven to be profitable, milkweed would provide an alternative that could facilitate the region's economic recovery. Another potential benefit would be import substitution. If the extraction problems were solved, milkweed could fulfill the U.S. demand for inositol, all of which is imported. Milkweed triterpenoids could substitute for some imported oils or waxes and for all domestically produced and imported pectin.

Although development of milkweed as a crop would have many benefits and at this stage has some promise, many economic, technological, agronomic, and ecologic problems must be resolved before it could be a commercially viable crop. Its potential will have to be examined in relation to present crops as well as new arid- and semiarid-land crops being studied.

INSECT REPELLANTS, ATTRACTANTS, AND TOXICANTS FROM ARID/SEMIARID LAND PLANTS

From the time of the early Romans until 1900 only three efficient plant-derived insecticides—pyrethrum, hellebore, and nicotine—have had widespread use. Advances in chemistry and improved screening techniques, however, have led to the discovery of many plant-derived insect toxicants, repellants, attractants, feeding deterrents, growth inhibitors, and sterilants since the turn of the century. Some of these active compounds may be developed commercially and would expand the range of available products for insect pest control. New plant-derived insecticides might provide substitutes for some synthetic insecticides that are ecologically disruptive and for others to which insects have developed a resistance.

Arid- and semiarid-land plants are good sources of insect toxicants and related compounds. Some of these biologically active chemicals are produced by the plants as defenses against pests and pathogens. In environments of climatic stress where plant growth is slow, insect attack can be particularly debilitating to a plant. A strong defense system may be critical to survival and probably has been an important factor in the evolution of arid/semiarid-land plants. Not only are these plants good sources of insecticides and related chemicals but they are adapted to areas that are marginal for production of traditional food and fiber crops. Arid/semiarid-land plants with commercial potential offer the opportunity to expand agriculture on land that is unproductive for established crops. In addition, perennials such as the neem tree or mamey apple may be ecologically preferable to other crops on arid and semiarid lands which commonly are highly susceptible to erosion.

The USDA Biologically Active Natural Products Laboratory in Beltsville, Md., has been studying plants as potential commerical sources of insect toxicants, deterrents, and attractants. Seven plants appear to be particularly promising. Most of these plants have been used locally in different countries for various purposes including insect control. The plants represent potential multiproduct crops for the United States and developing countries. Most of the work done by USDA has been on extraction and application of the chemicals. A great deal of applied research on agronomy, commercial processing, and marketing is needed before commercial production of most of these species would be possible.

Calamus

Calamus, *Acorus calamus,* is a semiaquatic perennial that can grow on dry land. The roots have been used from ancient times in India and Japan for the treatment of a variety of ailments and as an insect repellant and toxicant. The different varieties—American, Indian, Japanese, and European—have different insecticidal characteristics. Commercially available oils from the Indian and European varieties are obtained either by steam distillation or solvent extraction. They are repellent or toxic to clothes moths, house flies, fleas, lice, mosquitoes, and many stored-grain insects. The Japanese variety causes sterility in male house flies. Oil from the Indian variety is highly attractive to Mediterranean fruit flies, melon flies, and oriental fruit flies. The roots are used in China as an insecticide and vermifuge. The component primarily responsible for sweetflag's repellancy and sterility is B-asarone which can be synthesized more cheaply than it can be extracted from plants. It is effective against the rice weevil, probably the most damaging insect pest of stored grains. Another active component, asarylaldehyde, is commercially extracted from the plant material. These two compounds probably would be useful as fumigants for protecting stored grain from insects because they permeate grain-filled storage areas without leaving residues on the grain after the areas are ventilated. Other potential uses of *Calamus* compounds are for tuberculosis treatment, as a germicide, and in perfumery. One constraint to using *Calamus* chemicals is that B-asarone has a depressant effect on the central nervous systems of mice, rats, and monkeys. Although these pharmacological properties may limit use of *Calamus* oil to certain applications, they should not prevent use of the oil for agricultural insect control and possibly for medical purposes.

Big Sagebrush

Big sagebrush, *Artemisia tridentata*, is a multibranched perennial that is the dominant plant of the Great American Desert. It has been cultivated in the West since 1881 as a fodder plant for range cattle. The brittle branches sometimes are used for thatch by Indians, the seeds are ground into a meal by the California Indians, and a pollen extract is used against hay fever. In the past, *Artemisia* has had various insecticidal uses. For example, sagebrush leaves and shoots were placed in granaries to protect stored cereals from weevils and other pests, and the water in which they were steeped was used to kill or repel insect larvae, fleas, and locusts. An extract from sagebrush is effective as a feeding deterrent against the Colorado potato beetle, a pest of growing economic importance. This pest's resistance to insecticides applied in potato-growing areas is an increasingly serious problem in several areas of the world, and this resistance probably will become more common. Only one of the compounds responsible for the feeding deterrent activity has been identified. It has not been synthesized and it is unlikely that synthesis would be economically feasible. However, the crude, unpurified extract could be sprayed directly on crops, although the potential ecological effects of doing so must be assessed first.

Neem

Neem, *Azadirachta indica*, a common tree of dry scrub forests in India and Burma, grows on poor soils in hot, dry areas. Although all parts of the tree are repellent to insects, extracts of the seeds are outstanding as repellents and feeding deterrents for a broad spectrum of economic agricultural and household insects (e.g., Colorado potato beetles, Japanese beetles, scale insects, cotton bollworms). Seed extracts deter at least 25 species of crop pests in the United States from feeding, inhibit the growth and development of others, and render others sterile. These compounds seem to be nontoxic to man, animals, and plants. Because they are absorbed by the plant tissue, they offer relatively long-lasting protection to crops even after rain showers of high intensity. Three antifeedants have been isolated from neem. The most potent is effective against a variety of insect pests native to the United States. This chemical cannot be economically synthesized because its structure is so complex, but it can be extracted in pure form.

Neem is a source of many potential products in addition to insect antifeedants and repellants. Almost every part of the neem tree is used medicinally in India. Oil can be extracted from the seeds for soap, wax, lubricants, and lighting and heating fuel, and the residue can be used as an organic fertilizer. Other parts of the tree are used in various countries for commercial products, including timber and cabinetry wood, tannins, a toothpaste ingredient, and livestock fodder. Neem production could sustain cottage industries in Asia and Africa and provide a base for large commercial operations in the United States and Central and South America.

Neem plantations have been established in northern Cameroon, Nigeria, Gambia, India, Honduras, and some Caribbean islands. The U.S. Peace Corps is encouraging neem cultivation in Cameroon and Gambia, and USDA has started a program to develop neem commercially in Puerto Rico and the U.S. Virgin Islands. Constraints to commercial development include short-term seed viability, rapid photodegradation by sunlight of the major active principle after field application, unpleasant smell of the seed oil, frost susceptibility, poor growth on poorly drained soils, and poor agroforestry potential because of interference with other crops and vice versa. Despite these constraints, cultivating and processing neem seem promising. USDA is carrying out the major basic research on extraction and application of the chemicals. Universities and government agricultural institutes in India are focusing on applied aspects (i.e., agronomy, product uses, marketing) of commercially developing neem.

Heliopsis Longipes

Heliopsis longipes, a perennial herb in the aster family, is native to Mexico. *Heliopsis* roots have been used locally in Mexico as a spice, medicine, anesthetic, painkiller, and an insecticide against warble larvae found in cattle wounds. Root extracts have also been effective against houseflies, mosquitoes, body lice, bean weavils, and other household and agricultural pests. The active ingredient has been isolated, identified, and prepared synthetically, but extraction is more economical than is synthesis. Some transplanting and cultivating experiments using wild plants have improved plant biomass yields. However, in spite of the succulent character of the roots, they dry out when exposed to air and will not grow when transplanted. Therefore, care must be taken when transplanting wild plants that the roots are kept moist or plants are replaced immediately.

Mamey

Mammea americana is an edible fruit-bearing tree found in Latin America and the Caribbean. The flowers, fruits, seeds, and leaves are effective against a wide variety of insect pests including melonworms, fleas, ticks, lice, fall armyworms, mosquitoes, and cockroaches. Two major insecticidal compounds have been isolated and identified, and methods to extract them have been developed. People have used the plant for many other uses, but no serious attempt has been made at export or commercial production. The wood is used in construction and cabinetmaking; the flowers are used to make a liqueur in the French Antilles; the fruit is eaten raw or is stewed and made into a drink or candles, and gum from the bark extracts chiggers from the feet. The tree is cultivated on Caribbean islands, and in Mexico and Central and South America for the edible fruit. *Mammea's* potential as a commercial crop in southern Florida, Puerto Rico, and the U.S. Virgin Islands should be investigated.

Basil

In addition to its widespread use as a spice, *Ocimum basilicum,* or sweet basil, is recommended for use against gastric disorders, malarial fevers and skin diseases, and for insect control. The oil from basil is an effective repellant and larvicide for mites, aphids, and most species of mosquitoes; a growth inhibitor for milkweed bugs; and an attractant for fruit flies. Most repellant compounds in the oil have been identified. The oil content of plants varies depending on soil fertility and weather immediately preceding harvesting. Because extraction is simple and inexpensive, synthesis is not commercially practical. The plant is cultivated easily and can be grown and its oil produced in many places in the United States.

Mexican Marigold

Tagetes minuta is an annual that is native to Central and South America but also grows in parts of East Africa, India, Eastern United States, South Africa, and Spain. The oil produced by the seed, leaves, and flowers is strongly repellent to blowflies and is useful in the Tropics as a blowfly dressing for livestock. The leaves are used locally in Africa and India to repel mosquitoes and safari ants. The oil is more toxic to mosquito larvae than DDT. The plant also has potential medical uses and the roots exhibit fungicidal and nematocidal activity. An extraction method for the essential oil has been developed. Although two larvicidal compounds and the growth deterrent can be synthesized, laboratory synthesis of several of the pesticidal compounds gives low yields and unreliable results. Because large-scale cultivation of the plant should be feasible, extraction of the essential oil seems to have the greatest commercial potential.

COMMERCIAL PRODUCTS FROM MARINE PLANTS

Marine plants are represented both by seaweeds, macroscopic forms that mainly live in shallow coastal waters, and by phytoplankton, free-floating, widely distributed unicellular plants. Although a few flowering plants (angiosperms) are abundant in shallow waters, the majority of marine plants are algae, typified by their lack of a vascular system. Taxonomically, algae are highly diverse. Their highly specific coloration has served as a basis of classification; marine algae are divided into at least 12 distinct groups based on color (e.g., red seaweeds, brown seaweeds, blue-green algae, etc.). While no precise estimate has been made, it is thought that well over 100,000 species of marine algae exist. Biogeographically, marine algae live in all parts of the ocean and frequently are found in extremely high concentrations. Although precise figures are difficult to substantiate, the primary productivity of 1 acre of the marine environment may be twice that of a Midwest cornfield.

Marine plants have evolved unique and highly specialized biochemical pathways to adapt to their unique seawater medium and survival pressures. The marine environment is rich in chloride and bromide salts and other chemical entities such as sulfate. Marine plants use these elements in biosynthetic processes to produce compounds that are unique to the marine environment. Many marine plants have evolved toxins and deterrents as protection against abundant and freely migrating predators. Even though the same evolutionary pressures have produced similar responses in terrestrial plants, the defensive chemicals from marine plants are novel and represent interesting new chemical species that are unprecedented in terrestrial sources. Other chemicals represent adaptations to the physical environment such as wave shock and motion. For example, complex polysaccharides (complex sugars) act to reduce the surface tension of seawater. These constituents, too, are highly specific to marine algae.

Marine algae have been used in different countries for a long time as sources of foods, food thickeners and flavorings, animal fodder, soil manure, potash, and herbal medicines. For example, "Nori" and "Wakami" have become integral parts of Japanese diets, and over 18,000 tonnes of Nori are commercially produced each year. Numerous species of marine algae are used in China as herbal medicines to treat many maladies ranging from intestinal problems to sunstroke.

A classical use for seaweeds has been the extraction of halogens and potash. Brown algae were used for several decades as the major source of iodine, and the red seaweeds were used occasionally for deriving bromine. The U.S. Pacific coast between 1910 and 1930 was the site of a flourishing potash industry based on the high potassium concentrations found in local brown algae. The uses of marine algae as sources for elemental halogens, potash, and crude food-thickeners largely were curtailed by the mid-1900's as other, more cost-efficient sources were developed. But also during this period, many currently used algal products, particularly algal polysaccharides, became established.

A well-established industry in the United States now harvests marine seaweeds and extracts agar, carrageenan, and alginate. Agar is found in many species of red algae and is used mainly as a gelling agent and thickener in foods but also as a biochemical adsorbent, culture and nutrient medium for bacteriological research, and major nutrient medium for the industrial production of antibiotics. Carrageenan, which is also extracted from red algae, has widespread use within the food industry. The total annual market value of polysaccharides derived from red algae is about $200 million. Alginate, extracted from brown seaweeds, is particularly valuable for incorporation into industrial products and processes. It is used for its thickening, emulsion stabilization, and gelling properties.

Even though the majority of marine algal products come from the readily collected macroscopic forms, several products are being produced by the culture of unicellular forms. The green alga *Dunaliella*, for example, recently has been established in mass culture as a commercial source for glycerol (glycerine) and the orange pigment beta-carotene. Glycerol is used in the manufacture of many products (e.g., printing ink, antifreeze) and beta-carotene is used to impart color and provide vitamin A in animal feeds and human foods such as margarine and is also used as a sunscreen agent.

Several algal species have been used consistently in the biomedical sciences. In particular, active components of red algae *Digenia simplex* and various *Chondria* species are extracted, purified, and marketed as drugs in Asia. No other examples of successfully algae-derived pharmaceuticals exist, but there certainly is a great potential for further development in this area.

Even though relatively little *basic* chemical research has been performed on marine algae, mass culture techniques, both in the ocean itself and in controlled coastal facilities, have great potential to provide industrially significant quantities of marine algae. Funding from the Department of Energy (DOE) through the Solar Energy Research Institute (SERI) and several other agencies has supported work on requirements for effective algal growth. Marine algae probably will be a focus of considerable attention over the next decade as we investigate new resources for both energy and industrial product development.

Although relatively few algal products have been developed successfully by industry, the potential for the discovery and development of a plethora of unique new products seems unlimited. A few of the most notable areas for exploitation in the near future are summarized below.

Biomass Conversion

Work already has begun on assessing algae as sources of biomass for conversion to methane gas, ethanol, and other useful chemicals. Algae are efficient photosynthetically and are cultured conveniently in the open ocean, ponds, or controlled culture vessels. However, problems with fertilization of cultured seaweeds must be solved. Biomass conversion processes are not cost efficient, but continuing research is needed so that the technology will be available when required in the future.

Pharmaceutical Development

Although numerous biomedical uses for algal polysaccharides have been established, the majority of applications involve use of their physical properties rather than their physiological activities. A surprising percentage of algal polysaccharides, however, show antiviral activity. For example, a red seaweed extract contains an antiviral compound that is effective against *Herpes simplex*, a virus responsible for a disease that has reached epidemic proportions in the United States. Several substances with antibiotic and antitumor activity have been isolated from macroscopic seaweeds. Although few comprehensive studies of microscopic algae have been reported, some of these algae exhibit antimicrobial activities and are known to produce powerful toxins. However, almost no information exists on the pharmacological potentials of the tens of thousands of microscopic marine algae mainly because of the difficulty in purifying a single species of unicellular algae and growing it for biomedical studies. Much could be learned from such research.

The slow rate of developing new marine pharmaceuticals clearly can be linked to the limited involvement of the major pharmaceutical companies. Pharmaceutical firms do not have in-house expertise and marine biological laboratories in the past have not employed scientists with biomedical expertise. This is changing, however. Major programs have developed under the Department of Commerce's Sea Grant Program. The Sea Grant effort in biomedical development is an effective blend of academic and industrial (basic and applied) research that is yielding fruitful results. The Sea Grant project, "Marine Chemistry and Pharmacology Program," at the University of California, for example, has discovered more than 75 pure compounds with potential biomedical use and the project has emphasized collaboration with the pharmaceutical industry. This collaboration is the vital link to ensure that basic marine research finds its way to the industry that is **capable** and **interested** in developing new products.

Other governmental agencies have had more limited involvement in marine biomedical development. For example, the National Cancer Institute has dedicated significant resources toward the isolation of new antitumor drugs. Here again, the need to involve basic marine scientists to locate, identify, and quantitate suitable marine species for study was underemphasized, and considerable difficulties were encountered.

Agricultural Chemicals

Many synthetic pesticides are halogenated compounds. Since halogenation is a natural process in marine plants, the compounds produced are likely to possess agrichemical activity. Initial collaborative investigations indicate considerable promise. Of 12 algal compounds assessed in herbicidal and insecticidal bioassays, 9 showed some activity, and 1 was nearly equivalent to DDT in insecticide activity.

Here again, the success in developing marine algal agrichemicals lies in developing a close relationship between academic and industrial research. A limitation on commercial development of marine extracts is that little Government funding is available outside of USDA. Agricultural research funding should be expanded in the United States to include a greater component of academic research.

Food and Food Products

In addition to agar, carrageenan, and alginate, marine algae are recognized sources of numerous useful food products, including cooking oils. Although the seaweeds usually are low in protein, many phytoplankton are rich protein resources. The blue-green algae are potential protein resources, and one blue-green algae, *Spirulina,* has already been marketed as a health food.

Enzymes

Marine enzymes, while almost completely unknown, could be used beneficially in industrial processes.

Industrial Chemical Feedstocks

Both macroscopic and microscopic marine algae could be cultured to yield hydrocarbon mixtures that could be used as diesel fuel without further purification. Other compounds found in most marine algae could be used in the plastics industry. Notwithstanding the work on agar, carrageenan, and alginate, phytoplankton, in general, have been virtually unexplored for their polysaccharide components even though it is highly conceivable that they could yield new and important products.

Needs for Developing Marine Algal Resources

Small-volume products, such as a specialty pharmaceutical, could be developed from naturally occurring populations but, in general, effective use of marine algal resources, especially unicellular algae which cannot be collected in pure form, must be coupled with mass culture technology. Mass algal culture and product derivation should be developed keeping in mind multiple-product development. The algal resources that should be considered for development are those that produce more than one marketable product to offset the relatively high production costs.

A basic problem in considering development of marine algal resources is that there has been insufficient research on potential products from algae. Although a significant number of chemical investigations have been conducted on seaweeds, there have been few on unicellular algae. Considerable resources are being devoted to developing algal-culture technologies, but generally these studies are not predicated on a solid knowledge of algal chemistry, genetics, nutrition, and reproduction. In addition, mass culture techniques must be refined.

Biotechnological advances, particularly in the field of marine genetics, can be expected to have sizable impacts on use of marine resources. Marine products and biochemical processes are unique, and this unique gene pool could be highly useful in future product development.

A significant problem lies in the poorly developed working relationships between Government, universities, and appropriate industries. Government funding agencies have difficulty supporting applied research, particularly as it may benefit a single private enterprise. The university system finds its relations with industry strained by patent and proprietary information problems. Close cooperation between these entities will be necessary, such as has been developed by the Sea Grant Program. As this tripartite collaboration develops, it seems likely that marine algal species will become major sources of future products.

ANTICANCER DRUGS FROM THE MADAGASCAR PERIWINKLE

Although literature sources cite 3,000 plant species used or recommended for cancer treatment in different parts of the world, only one species has been used to produce a commercial cancer-chemotherapy drug. This plant is the Madagascar periwinkle, *Catharanthus roseus.* It is an herb or subshrub found throughout the Tropics and cultivated as a garden plant worldwide. The development of the periwinkle anticancer drugs from isolation and purification of several *Catharanthus* alkaloids to laboratory and clinical testing and subsequent marketing of two of them represents a tremendous success story in the field of plant-derived pharmaceuticals. In the short time since first clinical use, these alkaloids have become two of the most valuable cancer chemotherapy treatments available.

The Madagascar periwinkle was one of 440 plants selected for study in an Eli Lilly plant-screening program for plant-derived drugs. The plants were chosen on the basis of carefully assessed reports of folklore use and reported alkaloid contents. Alkaloids, complex nitrogen-containing plant compounds, are often physiologically active. They are the most common active ingredients in many plant-derived medicinals. *C. roseus* was reported to contain alkaloids and folklore uses indicated that it contained biologically active compounds. Past use of the plant had been based on its blood-sugar-lowering properties, suggesting to Eli Lilly researchers that it might provide a substitute for oral insulin. When tested at Eli Lilly, however, the plant initially did not exhibit hypoglycemic activity but did show strong and repeated antitumor activity when subjected to an antileukemia model. Ironically, the periwinkle had not been one of the 3,000 plants cited as cancer treatments in reports of folklore use.

Standard isolation and purification techniques were not successful in extracting the antitumor agents from the plant, so new extraction methods were devised. Using these new techniques (selective extraction followed by column chromatography and gradient pH technique), Eli Lilly isolated 55 alkaloids from *C. roseus.* A total of 74 alkaloids, 3 of which were previously unknown, have been isolated from mature periwinkle plants, and 21 additional compounds have been isolated from immature plants. This extraction work and subsequent sterochemical research to determine the alkaloids' chemical structures represent significant advances in the field of phytochemistry.

Two of the periwinkle alkaloids that showed potential as antitumor drugs have reached the marketplace. These are leurocristine (LC)-whose generic name is vincristine and is marketed by Eli Lilly as ONCOVIN-and vincaleukoblastine (VLB)-known generically as vinblastine. Although LC and VLB are closely related chemically, they have different potencies against tumors because of minor differences in their molecular structure. Leurocristine, called a "miracle drug" because it was placed on the market only 4 years after initial discovery and is extremely valuable in cancer chemotherapy, was responsible for a resurgence of interest in plants as sources of antitumor compounds. LC is most effective in treating childhood leukemia of the lymph system; alone it can induce a 50-percent response rate in children with acute lymphocytic leukemia, and in combination therapy gives a 90-percent response rate. It is also effective against a variety of human cancer, including Hodgkin's disease, breast cancer, and primary brain tumors. VLB is used mainly in treating lymph tumors, especially in Hodgkin's disease patients. It shows a 70- to 80-percent response rate in patients with lymphoma, is highly effective against testicular tumors, and shows activity against various other cancers.

These two compounds and other dimeric *Catharanthus* alkaloids showing similar antitumor activity represent a new class of antitumor agents. Although their mechanism of action still is not completely understood, it seems to be based on disrupting cell division, thus arresting tumor growth.

Chemotherapy treatments have improved over the last two decades so that they are effective alternatives for or additions to radiation and surgery as cancer therapies. Much of the improvement in chemotherapy is the result of combination drug treatments in which various drugs with different mechanisms of action are used together. The periwinkle alkaloids are important in these multidrug therapies and have been key elements in the increasing sophistication of cancer treatments.

The potential of *Catharanthus roseus* alkaloids as medicines is by no means exhausted. A great deal of chemical work has yet to be done both on LC and VLB and on the other periwinkle alkaloids showing antitumor activity. One alkaloid that seems particularly promising and needs more research is leurosidine. Clinical tests for an experimental leukemia model in mice indicate that leurosidine is the most experimentally active *Catharanthus* antitumor alkaloid. However, the yields from periwinkle plants are low and high doses are needed for testing, so sufficient amounts of leurosidine for comprehensive clinical trials have never been stockpiled. Another compound that has not been fully investigated is an unidentified chemical called "super leurocristine" which displays 300 times more antitumor activity than leurocristine/leurosidine fractions. This was never clinically tested and the high cost to stockpile the active fraction for testing now is considered prohibitive.

Chemical derivatives of *Catharanthus* alkaloids also deserve additional research. Since slight chemical alteration may produce dramatic changes in dose-limiting toxicity of a compound, work on chemical derivatives may uncover potentially marketable compounds with more benign side effects than the original compound.

Another area that should be explored further is the conversion of leurocristine to vincaleucoblastine. The yield of leurocristine from periwinkle plants is 0.0003 percent, the lowest yield of any commercially used medicinal alkaloid. The yields of VLB are considerably higher, and since the chemical structures of the two are closely related, it may be possible and economically beneficial to convert VLB into leurocristine. This conversion has been done successfully in the laboratory, but a great deal more work must be done before it can become a commercially viable operation.

Attempts to synthesize VLB and LC have been unsuccessful. This should continue to be a research priority. Until synthetic equivalents can be produced, the active compounds will have to be extracted from periwinkle plants. *Catharanthus roseus* plants were initially collected from the wild. As it became apparent that there would be a demand for thousands of tons of plant material, periwinkle cultivation began on farms in India and Madagascar. To avoid the risk that the supply of raw material might be cut off and to guarantee an uninterrupted supply of plants, cultivation was started in Texas.

The success of the work on the Madagascar periwinkle was dependent on two major factors: careful plant selection and the availability of an appropriate test system (an experimental mouse tumor) to monitor the effectiveness of purified active compounds. Plant selection was based on alkaloid content reported from folkloric use. Folkloric use can be a valuable indicator of the desired chemical activity if care is taken in interpreting the reports. If not, such reports can be misleading. Another method by which to choose plants for screening is random selection. The success of random selection could be improved by considering botanical and chemotaxonomic relationships between the plant to be tested and plants of known phytochemistry and biological activity. An experiment mouse tumor served as an appropriate biological test system to monitor the purified alkaloids for the desired activity.

Perhaps the major lessons to be learned from the research and development (R&D) of *Catharanthus* alkaloids as anticancer drugs are that pharmaceutical drugs can be obtained from renewable resources rather than petroleum-derived synthetics and the developing new plant-derived drugs can be profitable. Despite the potential of plants for providing valuable new drugs and high profits to the companies developing them, U.S. pharmaceutical firms have eliminated their plant-screening programs and the Federal Government has discontinued its program for plant-derived anticancer drugs.* This disinterest is not because the potential for finding valuable drugs in plants has been exhausted. Only a tiny proportion of the Earth's higher plant species has been phytochemically screened, and these species represent a bank of potentially important drugs. As already mentioned, more than 3,000 plants have been cited as possible anticancer treatments, not to mention known activity of numerous other plants that could be valuable for other medical uses. This disinterest in plant screening for pharmaceuticals is not universal. The Germans, Japanese, Russians, and Chinese have major investments in exploring potential plant sources for pharmaceuticals and other chemicals. Perhaps the reasons for the neglect of this research in the United States should be examined and decisions to discontinue work reconsidered.

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*See the paper by Farnsworth and Loub in the appendix.

STRATEGIC AND ESSENTIAL INDUSTRIAL MATERIALS FROM PLANTS

The United States depends on other nations for many materials and manufactured products important to U.S. industry, including agriculturally produced plant substances and mined materials. Some of these products are or could be agriculturally produced in the United States and used as industrial materials or as renewable replacements for petroleum as sources of feedstock in the chemicals industry.

Some industrial materials are classified as "strategic," or critical to national defense. Three "strategic" industrial materials are castor oil and sperm whale oil,* which are high-quality lubricants, and natural rubber. Law requires that sufficient supplies of these materials be acquired and stored in the United States to meet national defense needs in case of war. "Essential" materials are those required by industry to manufacture products depended on daily. Essential materials include items manufactured or extracted from plants (e.g., waxes, oils) and replacements for petroleum used as feedstock in manufacturing synthetic materials (e.g., plastics, chemicals).

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*The Endangered Species Act of 1970 prohibits production or importation of sperm whale oil so it is not stockpiled in the United States. A substitute for this high-quality lubricant must be provided. Jojoba is a promising substitute.

The United States imported an estimated $23 billion worth of agriculturally produced industrial materials and petroleum for feedstock during 1979. Average annual growth in imports for 1975-79 was 10 percent. The manufacture of synthetic organic chemicals consumed about 470 million barrels of petroleum as feedstock in 1978, valued at $15.1 billion. U.S. industry purchased nearly $2 billion worth of agricultural imports, $3.5 billion worth of newsprint and other paper products, and $2 billion worth of chemicals extracted from plants and petroleum.

Technologically, it seems possible to produce domestically nearly all the aforementioned imported agricultural products and materials and to substitute domestically produced agricultural products for the 470 million barrels of imported petroleum feedstock, with a net savings of about 270 million barrels of imported oil per year. Table 1 lists some of the potential domestic crops and what they might replace. Sufficient research indicates that their domestic production and use in the chemicals industry are chemically feasible, agronomically possible, and economically viable, although more agronomic and economic research must be undertaken before definitive conclusions can be drawn about their substitution feasibility. Production of only one-third the annual domestic demand for strategic materials would eliminate the need to stockpile them, could save at least $1 billion of public money over the next 18 years (otherwise spent in acquiring and maintaining strategic stockpiles of natural rubber and castor oil), and could provide replacements for sperm whale oil. Producing 100 percent of the strategic and essential industrial materials or their replacements might reduce U.S. foreign outlays by about $16.5 billion annually at constant 1979 dollars and demand levels.

Table 1.—Potential Domestic Crops and Uses

Guayule
Crambe
Jojoba
Lesquerella
Veronia-Stokesia
Kenaf
Assorted oilseeds
Hevea natural rubber, resins
High erucic rape oil and petroleum feedstocks
Sperm whale oil and imported waxes
Castor oil
Epoxy oils
Imported newsprint and paper
Petrochemicals for coatings and other industrial products

SOURCE: Office of Technology Assessment.

Production of substitutes for one-third to one-half the industrial materials purchased abroad would demand about 60 million acres of cropland. The United States has about 413 million acres of cropland and about 36 million acres of pasture and other land in farms that easily and inexpensively could be converted to crop production. Another 96 million acres of land could be converted to crop production with more difficulty and expense. The Nation's total cropland base (land capable of sustained crop production under intensive cultivation by known methods) is therefore about 540 million acres. According to USDA, about 462 million acres of cropland will be needed in 2030 to meet domestic and foreign trade demands for food and fiber. This would leave 78 million acres of the cropland base to meet other production needs. If 60 million acres were used for industrial and strategic materials production, 96.8 percent of the Nation's cropland would be used.

The question of land availability must be examined carefully. The land resource base that will be needed or available for food, fiber, and industrial chemical crops over the long term will depend on certain unpredictable circumstances including international trade (e.g., level of export sales, price of petroleum); changes in land productivity; and quantity and quality of agricultural land being lost to urban development, water impoundments, etc. Another issue is the feasibility of converting farmland and land in other uses to the production of industrial crops. Lands currently in agricultural production could be converted to industrial crops more easily than uncultivated lands and lands owned or operated by nonfarmers. It would be largely a question of the economic tradeoffs of one crop against another. If a new crop is sufficiently more profitable than an old one, it probably would be planted. However, the scant amount of information on motivations of persons owning farmland that is not farmed indicates that much of this land is owned for esthetic, recreational, or speculative purposes and could not be shifted into agricultural production easily. In this case, putting these lands into industrial crops is not a straightforward economic issue. The land would have to be leased or sold to farmers, and this transferral of landownership or control could be a constraint to new-crop development.

Another land-related question that should be raised is whether a 100-percent utilization rate of the agricultural land base is optimal. Serious thought should be given to possible land quality degradation, especially from cultivating marginal lands. Clearly, some agricultural lands could benefit from substituting a more ecologically suited crop for a traditional crop (e.g., crambe in areas marginal for corn or wheat), but care must be taken that increased use of the Nation's agricultural land base does not outpace development of appropriate cropping systems that minimize ecological degradation. In addition, the need for a land reserve that could be tapped in the event of unforeseen circumstances should be considered.

Current research on new crops is extremely limited. Only guayule, jojoba, and crambe are being grown on semicommercial scale acreages. Federal funding for research is greatest for guayule because of its importance to the military. However, the total 1981 public expenditures for guayule research totaled only $3 million. Research commitments to all other potential substitute commodities discussed here were considerably less.

Little additional basic chemical research is needed for these commodities. Chemical engineering to develop efficient, economical extraction and processing systems, however, is needed. Because of the present lack of risk capital in the private sector, public support of such research probably would be necessary if these plant materials are to be commercialized. However, in 1982, the Office of Management and Budget imposed rigid guidelines governing Federal research and directed USDA to terminate any ongoing research of a commercial nature. Byproduct-use research also will be needed to assess commercialization potential. The value of byproducts is unknown because information on their potential uses is limited.

The greatest need for research on these potential commodities in the immediate future is in the areas of plant breeding and agronomy. Most of these new crop materials being grown in research projects are from wild or nearly wild plants. Genetic improvements are needed to increase seed and oil yields and predictability of the plant under cultivation. Little agronomic research has been done for potential new commodities other than crambe and guayule.

The economic benefits of using domestic production to replace agricultural imports and to substitute renewable agricultural materials for petroleum as feedstock in the chemicals industry depend on:

- the relative costs of substitutes and current sources of these materials,
- the degree of profitability in producing new agricultural raw material, and
- the level of subsidization required by the agricultural industry to meet national strategic and essential materials needs.

One study of the commercial feasibility of establishing a domestic rubber industry based on guayule estimated that the price for imported rubber and the costs of domestic production will converge in the late 1980's, making it equally as attractive to produce the material domestically as to import it.

The primary consideration in substituting agricultural commodities for petroleum as feedstock in the chemicals industry is the price of petroleum. In industrial uses, seed oils could sell at a higher price per pound than petroleum without increasing the price of the final chemicals produced because these plants yield relatively pure chemicals that could be used with little processing. Extraction of the same chemicals from petroleum is complex and expensive. The economic viability of substituting agricultural commodities for petroleum cannot be assessed until semicommercial production and prototype-scale extraction are undertaken so that the values of the chemicals produced can be compared. Genetic improvement could make these substitutes more economically competitive.

During recent years, the Federal Government has spent between $7 billion and $14 billion annually to subsidize production of commodities that are already in surplus. If this subsidy were spent instead to encourage the domestic production of imported plant materials or to provide substitutes for petroleum feedstocks in the chemicals industry, the average subsidy on the 60 million acres required to reduce imports by half would fall between $116 and $233 per acre per year. If 60 million acres are used to produce such commodities, on-farm employment could increase by about 155,000 jobs. This also would generate indirect income and employment benefits to agriculturally related enterprises.

Evidence suggests that oil-conservation efforts in the United States and other importing countries already have had major dampening effects on world production and pricing. In the event the world oil price decreased as the United States switched to agricultural alternatives, the United States would have increased leverage with oil suppliers as long as its option to substitute agricultural commodities were kept open.

Domestic production of imported agricultural materials and petroleum substitutes would have foreign policy implications. Exporting nations would react unfavorably to U.S. import substitution, whereas other nations importing these materials would benefit from resulting lower prices. It would be important for U.S. domestic agricultural policy and U.S. foreign policy on import substitution to be consistent, and Federal policymakers would have to be cautious about geopolitical problems that might arise from Government support of import substitution efforts.

The key short-run issue for farmers, agricultural firms, and the Federal Government would be whether to subsidize production of new agricultural commodities instead of continuing to subsidize surplus production or support agreements to take land in surplus commodities out of production. Incentives for consumers of intermediate industrial materials and end-products to support substitution of domestically grown commodities would be lower cost, assurance of continued supply, and decreased price fluctuations.

Four domestic policy shifts would be needed to move toward domestic control and production of strategic and essential industrial materials:

1. from dependence on foreign nations for agriculturally based strategic materials to domestic supply of them;
2. to a national policy of encouraging agricultural research that has foreseeable commercial application, including participation with the private sector in commercialization activities, partly research and partly commercial in nature;
3. to spend Federal funds to support production of useful agricultural commodities rather than supporting production of surplus commodities or pay for farmers to discontinue production; and
4. to look at domestic production of agriculturally produced materials as a way of using our farm-production potential rather than depending on foreign trade.

Sufficient resources should be committed to the kinds of activities suggested here to use or discard, with just cause, the many development options that exist for domestic production of imported strategic and essential industrial materials.

INFORMATION USEFUL TO PLANT-DERIVED DRUG PROGRAMS

Higher plants are essential ingredients of a large proportion of U.S. prescription and over-the-counter drugs. From 1959 to 1973, new and refilled prescriptions containing plant products represented 25 percent of all prescriptions dispensed from community pharmacies in the United States. The dollar cost to the consumer for prescriptions containing active ingredients from higher plants was $1.6 billion in 1973. Adding an almost equal amount to this figure for plant-derived drugs dispensed from other outlets (e.g., out-patient hospital pharmacies, extended care facilities, Government hospitals), an estimated total cost to the consumer was $3 billion in 1973. The current annual cost to the consumer for plant-derived drugs is estimated to be at least $8 billion. In addition to the prescription drugs, the sale of herbal teas in the United States is estimated at about $200 million annually, and the sale of over-the-counter (OTC) drugs obtained from plants is probably at least $1 billion.

National Prescription Audit (NPA) data show that 41 species of higher plants yield all of the plant-derived prescription drugs. An additional 62 species of plants entered the prescription market in the form of crude extracts with active principles. Less than 50 pure compounds from plants were represented in the prescriptions analyzed. Virtually all of these compounds are produced commercially by extraction of plant material or by chemical modification of extracted plant compounds. Although most of these drugs have been synthesized, synthesis is not commercially feasible, with few exceptions.

Although much has been written in scientific journals of this country and abroad that should spark industrial interest to invest in research on plant extracts, interest in this country has declined. In 1974, the American pharmaceutical industry's total research and development budget for pharmaceuticals for human use was $722.7 million. Only one firm was involved in direct research to explore plants for new drugs with an annual program budget less than $150,000. Today, there are no U.S. pharmaceutical manufacturers involved in a research program designed to discover new drugs from higher plants.

Of the developed countries, only West Germany and Japan pursue development of new plant-derived drugs. West German studies are supported by many small firms but have not captured the interest of large pharmaceutical companies. Japanese academicians receive government and industrial support for research on plant drugs, and Japanese pharmaceutical firms have major research departments dedicated to the same goal. Scientific papers from Japanese research laboratories relating to drug-plant development outnumber those from the United States by at least tenfold, and Japanese patents for plant-derived biologically active substances outnumber those from the United States by a factor of at least 50.

Plant sciences have not had a voice in U.S. corporate or high-level governmental decision-making, except in the area of basic agriculture. Important decisionmakers connected with drug development apparently are unaware of the extent to which plants contribute to our source of drugs. During the past three or four decades, research administrators rarely have been trained in plant sciences. Further, science has advanced to a point where interest has not been on the intact organism—plant, animal, or microbe—but rather on the cell, cell contents, and cell biochemistry. Typical industrial drug development increasingly has involved synthesis of molecules based on structure-activity relationships, and natural product drug development has been restricted to antibiotic production by micro-organisms.

Most useful drugs derived from higher plants have been "discovered" through scientific inquiry into alleged folkloric claims of therapeutic effects, although in recent years the random collection of plants followed by pharmacologic evaluation has been pursued. A major program of the National Cancer Institute (NCI) involving the "screening" of plants randomly collected worldwide ended in late 1981. This program, which was started in about 1956, tested some 35,000 species of plants for antitumor activity in laboratory animals. Although a large number of highly active agents were discovered by the NCI program, some remain to be studied in humans and as yet none have been approved for use in humans by FDA.

Industry's development of useful drugs from higher plants during the past 30 years has not been more productive than Government efforts. Since 1950, pharmaceutical companies have produced only three plant-derived drugs that have reached the U.S. prescription market: reserpine, vincaleukoblastine, and leurocristine.* The total number of industry research dollars required to discover these drugs has been miniscule compared with the cost of placing synthetic drugs on the market. One reason for this might be that much of the unexplored flora in the world is found in tropical or semitropical developing countries that may be regarded as unstable supply sources for an international market. However, another country might serve as a source of wild plants or plant supplies may be obtained through cultivation or other techniques (e.g., tissue culturing). A second reason industry cites for lack of screening and plant-drug development is that patent protection is less secure with natural products than with synthetics. There is little evidence to back up this claim.

Data of value in organizing and implementing an effective plant-derived drug development program are difficult to obtain through available online drug data bases or from published reports. In addition, much of the useful pharmacological data on plant extracts were published prior to the earliest data covered by all available online data bases. Pharmaceutical companies are reluctant to share data derived from testing plant extracts, even if the data are negative and are of no commercial interest to the firms. Negative data are as important as positive data in a broad plant-based development program; knowledge of past negative research can help other researchers in selecting new plants for study without duplicating past work. NCI published negative data regularly at the beginning of the plant screening program, but this soon ended.

If plants to be screened for a plant-derived drug program are not to be screened randomly, they should be chosen on the basis of best available information (table 2). Information sources will vary, but probably would include:

1. *Ethnomedical data*—anthropological writings, folkloric writings, popular books, pharmacopoeias, etc.;
2. *Experimental data on plants*—abstracting services (e.g., *Chemical Abstracts*), bibliographic online data bases, review articles.

After collection of available pertinent data, drug development programs proceed through:

- plant collection,
- bioassay for evaluation of crude plant extracts,
- isolation and identification of biologically active chemicals from plants, and
- clinical evaluation and marketing.

Few pharmacologists are experienced in evaluating crude plant extracts or are interested in developing bioassay systems outside their own area of interest. Even though a program is designed to identify only one or two types of

Table 2.—Information To Be Included in a Data Base for Drug Development From Plants

Plant characteristics: Latin binomial effects claimed; common names; place of collection; geographic range; parts of the plant studied.

Ethnomedical uses: Crude plant material or type of extract used to prepare the dose; dose employed, administration, and dosage regimen; beneficial effects claimed; side effects reported.

Chemical constituents: Part of plant in which specific constituent is present; range of percentage yield of the chemical; data on seasonal or other variations in chemical quality or quantity.

Experimental testing: Type of solvent used to prepare extract; type of test (in vitro, in vivo, human study); test species (e.g., rodent, primate) and status; dose and route of administration.

Other information: References to compounds that have been partially or completely synthesized; studies of cultivation; effects of cultivation, processing, and storage on yield of useful active constituents.

SOURCE: Office of Technology Assessment.

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*See paper by Svoboda in the appendix.

biological activity, it would be cost-ineffective not to carry out as many bioassays as possible. Routine techniques are available for isolation and purification of active principles after bioassay-directed plant fractionation to enrich the biological activity; however, most existing compounds could not be separated economically from plants using the more sophisticated procedures. Efforts should be made to use simplified procedures so that high-extraction costs do not prevent commercial development. Clinical evaluation is expensive and complicated, requiring evaluation at several stages by FDA. The estimated total cost for developing a new drug depends on the costs for clinical testing, but would fall between $5 million and $35 million.

Ten computerized online data bases have information useful to a plant-derived drug development program (table 3). All but one are unable to compare, correlate, or analyze research data analytically; they are solely bibliographic. Ideally, one would desire a nonbibliographic file that could list and, by computer, compare or correlate real data contained in pertinent citations, then present the data in a digestible tabular form providing the citation sources. In 1975, NAPRALERT (Natural Products Alert) was initiated to overcome the difficulties in using existing files for developing research projects associated with natural products and drug development.

Approximately one-third of the citations now computerized in NAPRALERT represent retrospective searches of literature from the early 1900's to the present. The remainder cover current information. In addition to bibliographic information, NAPRALERT records the chemical constituents and pharmacological bioassay information from plant, microbial, and animal extracts. The accepted and synonymous nomenclature of the organism, the parts of the organism used in the study, and the geographic source of the material are important elements of the data base. NAPRALERT also records ethnomedical or folkloric notes as they are encountered in the literature.

This data base can be used to systematize random screening of plants through organized computer search and analysis of data to pro-

Table 3.—Data Bases Pertinent to Drug Development

Name	Developer	Contents
Agricola	USDA	Agricultural chemistry and engineering, food and plant science, nutrition and related agricultural fields
BIOSIS PREVIEWS	Biosciences Information Services	Life science for microbiology, plant and animal sciences, experimental medicines, agriculture, ecology, pharmacology, biochemistry, biophysics
CAB	Commonwealth Agricultural Bureau of England	Compilation of 20 agricultural science data bases; includes plant and animal breeding abstracts, plant pathology, nutrition, entomology, related fields
FSTA	Food Sciences and Technology Abstract	Agricultural chemistry, food science, home economics, patents
CACON	Cacon Chemical Abstracts Condensate	Most life sciences and physical sciences
MEDLINE	National Library of Medicine	Life sciences and/or medical information
IMEPLAM	Mexican Institute for the Study of Medicinal Plants	Natural history and folkloric claims for Mexican plants
—	Chinese University of Hong Kong	Retrospective and current literature citations and brief abstracts of Chinese publications on traditional medical practices
NAPRALERT	University of Illinois	Bibliographic information; chemical constituents; pharmacological bioassay information; plant names, parts and geographic source; ethnomedical information

SOURCE: Office of Technology Assessment.

vide a ranked list of the more probable candidates for study. Such a method using NAPRALERT was tested for a WHO Task Force assembled to identify indigenous plants potentially useful for human fertility regulation, identifying approximately 4,500 plants based on folkloric claims or laboratory experiments. Three hundred were identified as most promising for study through folklore information, pharmacological, and geographic data. Fifty have received preliminary laboratory investigation, and eight have confirmed activity but have not undergone clinical testing yet.

NAPRALERT has the capability to present in one computerized report all published information on folklore uses, biological activities (in vitro, in animals or humans), and chemical constituents. Together these data may suggest areas for research on new uses or applications of a specified plant or group of plants. They can also be used effectively to assess potential dangers or to suggest safeguards that should be employed when using certain plants.

While plants already are important ingredients of U.S. pharmaceuticals, they could be potential sources of many new chemicals for the drug industry. Despite this potential, pharmaceutical companies have discontinued plant-drug development programs. One reason they give for their disinterest is the high cost of developing a new drug. Any means of systematizing plant selection for screening by making data on past research and folklore use readily available would decrease research time and improve the chances of discovering a marketable drug. Ten automated data bases exist that can provide such information useful to drug development programs. NAPRALERT is the only nonbibliographic file and represents a unique data retrieval system of great potential value to drug development work.

USDA'S DATA BASE ON MINOR ECONOMIC PLANTS

The world has thousands of minor economic plant species which potentially are as important ecologically and economically as the dozen major agricultural species. There is an overwhelming number of climatological, pedological, anthropological, latitudinal, and biological variables associated with these minor species. The Economic Botany Laboratory (EBL) of USDA is trying to gather such data on these potentially useful species.

Seven data base files and their subsets are or have been online, and three prototype files have been developed. The online files can be linked to each other through scientific names to provide more complete information of species' characteristics. But funding has declined for this service in recent years; some files have been taken offline and others have ceased to grow with increases in available information.

Data Base Files

Ecosystematic File incorporates data from over 1,000 questionnaires mailed worldwide to scientists and extension people, intentionally emphasizing developing countries. Within 2 years some 500 people responded, sending published and unpublished ecosystematic data (annual rainfall, annual temperature, soil type, soil pH, elevation, etc.) on 1,000 species of economic plants, weeds, and nitrogen-fixing species. Each species in the file is recorded with the name and address of the reporting scientist(s), thus providing opportunities for more specific followup.

Yield File includes data from the questionnaires and from publications of experiment stations. The entries probably account for less than 1 percent of the yield data published annually by experiment stations. With increased funding, the data in this file could be increased, thus providing a means to compare yields of exotic crops (with various inputs) in ecologically similar areas.

Climate File includes monthly temperature and rainfall means for about 20,000 stations worldwide and the elevation of most of these localities. This file is the computer tape of Wernstedt's World Climatic Data, supplemented by information from publications and the questionnaire sent out by USDA. A continentality variable that compensates for seasonal temperature extremes of continental sites has been added to the file. This helps differentiate among climates with similar mean annual temperatures but different vegetational potential. A species' ecological amplitude can be determined by using this file in conjunction with ecological data for geographical areas from which the species is reported.

Where no data on climate are available, the presence of weed or plants with known ecological amplitudes of temperatures and rainfall can help predict climate in remote areas. Data on weeds' climatic amplitudes were added to this file under the Ecological Amplitudes of Weeds program. Another use of the Ecological Amplitudes of Weeds program is in mapping the potential for an alien weed to spread in the United States. Climates favorable to the spread of a weed can be located by determining ecological amplitudes of a weed through consulting its distribution and extracting climatic data from the Climate File.

EBL has formulas for converting its 20,000 climatic data sites into Holdridge life-zone maps for countries not now mapped in the Holdridge system. Standing biomass, total carbon, and annual productivity of the zonal forests can be projected from this information, giving real or projected yield figures for high-biomass grasses, energy-tree plantations, or conventional crops. This could provide some guidelines for choosing the best crop-agroforestry combinations for agricultural development in Third World countries.

Nutrition File includes at least one credible entry for each plant species in Food Composition Tables for East Asia, Africa, and Latin America. The plant's nutritive contents (elements, vitamins, calorie, and fiber content) are ranked extremely low, low, high, or very high relative to USDA's recommended dietary allowance (RDA). The Nutrition File (as-purchased proximate analysis or zero-moisture analysis) can be linked through a species' scientific name to the Yield File to convert yields of grain per hectare to yields of protein per hectare, and to the Ecosystematic File to show which will yield the most leaf protein per hectare under any specified combination of annual temperature, annual precipitation, soil pH, etc.

Ethnomed File was compiled to encourage Third World countries to supply medicinal and poisonous plants for a collaborative screening program with the U.S. National Cancer Institute. With 88,000 entries, the Ethnomed File is probably the largest extant computerized data base for folk cancer remedies. The file also covers general folk remedies and pesticidal activities. Ethnomed no longer is online but survives as a much consulted printout.

Prototype Data Bases

Agroforestry File includes different subfiles containing information on ecological parameters, germination requirements, nutrition values, cultural requirements, yields, wood characteristics, use, and plant pathology for several species considered for agroforestry. Perhaps the prototype file's greatest impact was to show that almost no data were available on most nonconventional economic plants.

Pest file has only about 2,500 entries listing the scientific name of the host plant, the plant part affected by the disease of insect, and the name and type of pest. Although this information is useful for predicting pest problems if the pest is known to be in the area chosen for introduction, it does not help predict the possible presence of the pest on the site. If the file were expanded to provide data on the ecological amplitudes of pests and diseases, it could help avoid or reduce the risk from pathogens or pests. This could launch a new phase in biological control of pests' "biological evasion." For example, where the host tolerated more cold than the pests, planting in the colder area might be advantageous.

Intercropping lists major and minor crop combinations, all species in pasture mixes, yield data, yield differentials, and cultural and other variables. By using the scientific names to link this and other files one could find out which crops have been tried around the world as intercrops. In densely populated Third World areas, intercropping clearly promises more quality, quantity, and/or variety of crops per hectare than monocropping.

Limitations to the application of the EBL data compilation program exist. In intermediate ecotypes, the effects of factors such as slope, soil porosity, soil type, vegetation cover, cultural conditions, insolation, prevailing winds, etc.,on plant characteristics may be significant. Few data are available and some of these variables are entered for only a few places. The 20,000 sites for which there is climatic data are not classified under a single soil-classification system. This prevents correlation of plants' ecological tolerances based on soil properties.

A major program would be needed to collate the Food and Agriculture Organization and/or USDA soil units with the 20,000 climatic data sites, soil pH, weeds, crops, yields, diseases, insect pests, and native perennials. This could be done for a large number of the 20,000 sites. This "International Plant Utilization Data Base" would develop ecological amplitudes and means and determine optimal conditions for all the economic species of the world and their pests and pathogens. Ancillary to this could be the development of an economic data base that includes transportation costs, shelf life, world demand, trends in production, and current price of a species. Crops that make the most sense economically then could be chosen from the many crops ecologically adapted to the area. Experimental data resulting from trials would be used to select the right species for that particular area and to augment and refine the data base. This capability of matching crops to their most suitable environment would be extremely valuable for use in both the United States and in developing countries. It would assist significantly in agricultural planning programs sponsored by international development agencies by suggesting best crop options for target environments. Use of the EBL data base could minimize crop-development efforts in environments that are marginal or unsuited to the crop species and help avoid or reduce the use of costly or ecologically disruptive agricultural inputs (e.g., energy, water, agricultural chemicals). In addition, it could help reduce the risk of spread of disease and pests.

Such a data base could select species best adapted to a given climate for whole-plant utilization schemes in which food, oilseeds, leaf-proteins, chemurgics, drugs, etc., would be the main products and biomass would be an energy-producing or commercial fiber byproduct. Greater plant use becomes more important as petroleum supplies—for energy and for transportation of products—become more scarce and expensive.

Without renewed funding these data bases have a short life expectancy. The cost of maintaining the files online is at least $10,000 a year before any programs are run on the data. USDA is a constant user; daily, scientists consult the hard copy generated by the EBL data base to answer questions on agronomy, agroforestry, climate, ecology, ethnomedicine, nutrition, pathology, and utilization. Many other U.S. Government agencies have benefitted from the files and could reduce future costs by consulting them.

IV.

Findings and Discussion

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OPPORTUNITIES

The potential for developing new sources of valuable plant chemicals is largely unexplored and the benefits from doing so unexploited. Of the Earth's estimated 500,000 to 750,000 species of higher plants, no more than 10 percent have been examined even cursorily for their chemical makeup. An even smaller number are grown commercially: only about 300 plant species worldwide and 100 species in the United States have been developed as crops for food and fiber products. In concentrating on a relatively few crops, other plants that could become important food and nonfood crops have been neglected. Plants are known sources of medicines, proteins, waxes, oils, resins, tannins, and other useful substances. Technologies to extract these chemicals are becoming more advanced, and developed whole-plant utilization schemes in which these substances are extracted and the residue used as a commercial byproduct or for energy production are receiving increased attention. Developing new crops and industries based on plant extracts and extraction residues provides opportunities for agricultural and industrial expansion that could benefit farmers, consumers, industry, and the Nation as a whole. New-crop and plant-product development could:

- diversify and increase efficiency of agricultural production,
- improve and possibly expand land resource use,
- offer increased economic stability to farmers,
- create new and improve existing agriculturally related industries,
- increase employment opportunities,
- provide consumers with new products,
- provide industries with alternative sources of raw materials,
- help supply the country with strategic and essential materials, and
- improve the Nation's balance of payments through import substitution.

Some of the greatest benefits of new-crop development would result from crop diversification. As already pointed out, the U.S. agricultural system is based on a limited number of crops. Because agricultural research and development efforts on these crops have contributed to their increased productivity, over-production has become a regular feature of American agriculture. Federal price support programs and production limitation programs designed to protect farmers from depressed commodity prices are costly. The Congressional Budget Office predicts that agricultural price support programs will cost the Federal Government at least $21 billion in 1983 alone. Alternative crops could help shift production away from traditional crops and into new crops, thus increasing economic opportunities for farmers and reducing Federal farm-support programs.

The concentration of U.S. agriculture on a small number of major crops invites economic instability. The economies of many agricultural areas are based on one or a few crops commonly grown in monocultures, leaving farmers vulnerable to the effects of pests and changing market conditions. New crops could provide alternatives to traditional crops and opportunities to develop new agronomic systems such as multiple-cropping or intercropping. Production of two or more crops offers an economic buffer in the event that one of the crops fails or the market price drops. In addition, the development of whole-plant utilization schemes in which many commercial products are available from one crop offers farmers greater economic insurance against price fluctuations than if they depended on a single product from a crop.

Widening the crop base also would enable the farmer to choose a plant species best suited to local agronomic conditions. U.S. agriculture has been largely manipulative; farmers have modified the land resources to conform to a particular crop. An improved match of crop and resources could help reduce increasingly expensive and scarce inputs of energy, chemicals, and water. For example, assuming that markets for its products can be successfully developed, milkweed, a semiarid-land plant, is a potential substitute for irrigated crops now grown in the western Great Plains where ground water resources are being depleted. Similarly, crambe, another dryland crop, might be more effectively grown than corn or wheat in dry areas marginal for these crops. Plants ecologically adapted to a site might require smaller inputs of pesticides than crops without built-in chemical or biological defenses against local pests.

Widening the crop base might also increase U.S. cropland acreage. If developed, new crops that could be cultivated on marginal lands without large amounts of chemicals, fertilizers, and irrigation water offer the opportunity to extend production to these lands that are unable to support traditional crops. Plants that might be cultivated on arid lands, in areas where the soils are highly alkaline, and on reclaimed strip-mined lands should be investigated. Benefits resulting from cultivating such lands include increased farming opportunities and stimulation of industrial production in economically depressed areas.

New crops could provide the consumer with a wide range of new products, including medicines; essential oils for cosmetics, spices, and drugs; detergents; vegetable dyestuffs; and insecticides, to name a few. One striking example of new plant-derived products is the highly effective anticancer drugs extracted from the Madagascar periwinkle (*Catharanthus roseus*) plant. The endod plant (*Phytolacca dodecandra*), which contains a potent molluscicide, is another example of a plant that may provide great human health benefits. Although it is still being tested, this molluscicide might prove to be important in the control of schistosomiasis, a tropical/subtropical disease affecting 200 million to 300 million people.

Plant-derived insect toxicants, repellants, attractants, and various biocidal compounds constitute another important group of extracts with potential commercial value. These plant extracts offer alternatives to some synthetic compounds that have negative and long-lasting ecological impacts on the environments in which they are applied. A variety of these natural biocides can be extracted from arid- and semiarid-land plants, including neem tree, sweet basil, and sagebrush. Producing such crops could improve or extend cultivation to lands that are often unproductive for U.S. food and fiber crops. These products could be particularly effective for pest control where other arid/semiarid-land plants are being cultivated.

Just as arid/semiarid-land species represent a group of plants with largely unexplored production and product possibilities, marine plants have been relatively untapped as sources of commercial products. Except for extracting agar, carrageenan, and alginate for the food industry, little commercial processing of marine algae is done in the United States. Research in the relatively new field of marine phytochemistry has revealed that marine algae are sources of unique chemical compounds. Certain marine algae show potential as sources of pharmaceuticals, agricultural chemicals, food and food products, enzymes, and chemical feedstocks. Multiple-product development seems promising. With improved mass culture techniques, large-scale production of algae in the ocean and in controlled coastal facilities may be feasible. Development of marine algae for commercial products provides new opportunities to expand the U.S. production base and develop related industries.

New crops could be sources of industrial raw materials such as oils, waxes, gums, fibers, and chemical feedstocks. These raw materials could stimulate the development of new industries and enable existing firms to expand their product lines. Because many of the plants being researched would be cultivated on marginal lands, resulting industrial expansion would occur in places that commonly are economically depressed. These industries could stimulate local employment opportunities not only in the agricultural but in the industrial sector.

Domestic production of plant-derived chemicals could have a beneficial economic impact through import substitution. The United States imported an estimated $23 billion worth of agriculturally produced industrial materials and petroleum for industrial feedstocks in 1979. Domestic crops that could provide direct substitutes for agricultural products or alternative chemicals to petroleum as fuel or industrial feedstocks conceivably would be important in import substitution and for foreign exchange savings.

Domestic production of substances considered strategically important to the Nation or essential to U.S. industry should be encouraged. There are obvious advantages in promoting self-sufficiency, guaranteeing a ready supply, avoiding stockpiling, and reducing reliance on stockpiled materials. Research is being carried out on plants that can serve as sources of industrial and strategic materials and as petroleum substitutes. Certain materials of national strategic importance are required by law to be stockpiled. Listed among strategic materials are castor oil, an important industrial coating and lubricant; sperm whale oil, a heat-resistant liquid wax whose primary strategic use is as a lubricant in jet engines; and rubber.

Half the rubber used in the United States is synthetic; the remainder is natural *Hevea* rubber. The United States imports all its natural rubber at an annual expenditure of $1 billion, making rubber the Nation's second-most-expensive import after oil. The United States could reduce significantly its dependence on foreign sources of rubber by producing it domestically. Because of its importance to the military, the Federal Government is funding research on guayule, a desert plant that is a promising substitute for *Hevea* rubber. Guayule is being studied as a potential crop and is being grown on small commercial acreages in the Southwest.*

Jojoba (*Simmondsia chinensis*), also in limited commercial production in the United States (about 20,000 acres), is a potential substitute for sperm whale oil. Use and importation of sperm whale oil was banned in the United States in 1970 under the Endangered Species Act. Another possible substitute for sperm whale oil is a chemical extracted from meadowfoam (*Limnanthes douglasii*), now being studied at the Department of Crop Science at Oregon State University. *Limnanthes* oil can be converted to a liquid wax that has properties similar to jojoba oil.

Castor oil is extracted from castor beans grown in Brazil. Although castor beans have been produced in the United States, a substitute oil is being sought because castor beans have toxic and allergenic properties that are hazardous to humans and animals and pose waste-disposal problems. A possible substitute oil can be obtained from *Lesquerella* species, members of the cabbage family that can be grown in the United States.

U.S. stockpiles of natural rubber and castor oil are far below the level required by law. Acquiring, maintaining, and storing these strategic stockpiles would cost the United States an estimated $1.1 billion (in 1979 dollars) by 2000. Domestic production of substitutes could help eliminate the need to stockpile natural rubber and castor oil.

The United States depends on other countries to supply a major portion of its demand for petroleum. The interest of the U.S. Government and the chemical industry in domestic production of plants for fuel and chemical feedstocks has increased as a result of the rise in petroleum prices since the 1973-74 Arab oil embargo. Researchers at the USDA Northern Regional Research Laboratory in Peoria, Ill., are investigating several plants as potential petroleum substitutes. Oils or fatty acids from seeds of certain plants may provide substitutes for petroleum-derived chemicals and some botanochemicals. New oilseed crops are found at a variety of stages of development. Preliminary chemical and botanical investigations have indicated crop potential of *Cupea* species as sources of lubricants and detergents, *Veronica* species and Stoke's aster (*Stokesia laevis*) for manufacture of industrial coatings and plastics, and *Lesquerella* species as sources of sub-

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*Guayule was grown in the Southwest United States during World War II as a substitute source of natural rubber when imports were cut off. After synthetic rubber was developed and *Hevea* rubber trade was restored after the war, production of guayule in the United States was discontinued.

stitutes for castor oil. More extensive basic and applied research has been carried out on two other promising species: meadowfoam and Chinese tallow tree (*Sapium sebiferum*). Small amounts of jojoba (about 20,000 acres) and crambe (*Crambe abyssinica*) are further along in their development as new crops; they are being grown commercially on small scales.

Fuel crops under study fall into four categories: oilseeds, hydrocarbon crops, starch/sugar crops, and biomass plants. Oilseeds could provide diesel fuel; hydrocarbon extracts could be cracked to produce gasoline or liquid fuels; starch/sugar crops are used in alcohol production; and biomass crops could undergo alcohol fermentation, gasification, or direct burning.* Research funding available through USDA, the Department of Energy, and the National Science Foundation (NSF) has supported work on milkweed (*Asclepias spp.*), buffalo gourd (*Cucurbita foetidissima*), and gopher plant (*Euphorbia lathyris*) as potential energy crops. Because these and other potential fuel crops could be grown on arid or semiarid lands, they would not compete with food and fiber crops for prime agricultural land. Further technological, ecologic, and economic analyses are needed before these plants could be developed as commercial sources of fuel.

In summary, the development of new crops for plant extracts offers many potential social, economic, and ecologic benefits on both local and national levels. New-crop development could benefit agriculture through crop diversification, expansion of the land resource base, and increased efficiency of crop production (e.g., rotation and multiple-cropping systems); industry through product diversification and raw material availability; consumers through provision of new products and increased employment opportunities (on-farm and industrial); and the Nation through reduction of agricultural price support programs, import substitution, and independence from foreign sources of strategic and essential industrial materials.

Successful introduction and establishment of a crop, however, require a long and adequately funded period of coordinated R&D. Each potential crop would be faced with a unique set of technical and economic constraints that could threaten its commercial development. The field of new-crop and plant-product development on the whole faces some general constraints. These will be discussed below.

CONSTRAINTS TO NEW CROP DEVELOPMENT

Potential crops require many years of agronomic research and product development balanced with market development for successful introduction. This involves a long chain of R&D steps including selection of plant species (involving chemical and biological characterization); isolation and purification of desired compounds; crop development (including genetic improvement, agronomic research, and harvesting technologies); transportation and storage; processing technologies; and marketing. (Plant-derived pharmaceuticals, biocides —e.g., insecticides, fungicides—and foods for human consumption—e.g., proteins, vegetable oils—require additional research because before marketing they must be tested in compliance with FDA regulations to ensure that they present no health or environmental hazards. Clinical testing for pharmaceuticals is particularly expensive and time-consuming.) Once a product is marketed, further research on agricultural practices, processing, and marketing would be required to fine-tune on-farm and industrial techniques. The future of new-crop development for plant extracts will depend on the existence of appropriate R&D systems that can facilitate breakthroughs and continued improvements.

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*For more information see OTA 1980 report *Energy From Biological Processes*, and OTA 1979 technical memorandum on gasohol.

Many constraints to developing new crops and plant extracts industries are encountered at the four major steps in the development process—namely:

- research,
- crop production,
- industrial processing, and
- marketing.

The following discussion examines problems and potential impacts of new-crop/plant-product development at each stage.

Research

Developing a new plant-extract industry requires research in a number of disciplines, including chemistry, botany, genetics, agronomy, entomology, engineering, and marketing. Expertise in all these fields is rarely concentrated in one institution. For example, most agronomy research is carried out in public, land-grant institution, and USDA, whereas industrial biochemistry and engineering expertise is primarily found in the private sector. Both the private and public sectors depend on the foundation of basic science provided by university researchers. Clearly, coordination of research efforts of Federal and State Governments, universities, and industry is essential if new crops and plant extract products are to be developed efficiently.

Agricultural research in the past has focused on improving yields of existing U.S. crops or on crop improvement of introduced plants. Only within the last decade has much effort been directed toward developing new crops for plant extracts in the United States. Although scattered plant screening and crop development projects in the United States have demonstrated the potential for crop and product diversification, work in this field and support for it remain limited and sporadic. The limited attention of industry is focused mainly on industrial feedstocks. Industry's lack of interest in plant-derived pharmaceuticals is notable.

Funding for new-crop development is only a small portion of USDA's research budget. Combined State and Federal (USDA) appropriations for agricultural research in 1983 total about $1 billion, most of which will be spent on the country's well-established crops. The share of new crop research within USDA's Agricultural Research Service (ARS) is only $3 million this year.* An estimated additional $3 million to $4 million is being spent this year on such research by NSF and other Federal agencies. When research funding is cut, work on new crops often sustains the heaviest budget reductions, losing out to established crops. Ironically, while research on new crops, which offers opportunities for crop diversification and new markets, remains underfunded, the costs for Government price-support programs for overproduced crops continue to expand.

Recent cuts in Federal support for applied research have been made on the premise that the private sector should play a larger role in applied research, freeing public moneys for basic research. At the same time, however, nondefense Federal agency research budgets and appropriations for universities and competitive grant programs, particularly in the life sciences, have been cut, reducing support for basic research.

If the private sector is to play a larger role in research, it must be both able and willing to invest. Within the private sector, venture capital and multinational corporations are most likely to take the initiative in developing new plant products. Multinationals with well-established research branches might be able to expand research efforts to fill gaps in basic research left by Federal cutbacks in research. The private sector, however, tends to wait until enough basic and applied research has been done to demonstrate profit potential before investing in further research. Once profit potential is established, the private sector becomes much more willing to invest in product R&D.

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*ARS research on new crops was carried out in Phoenix, Ariz.; Pasadena, Calif.; Bryon, Ga.; Tifton, Ga.; Peoria, Ill.; Ames, Iowa; Beltsville, Md.; East Lansing, Mich.; Mayaguez, P.R.; and Lubbock, Tex. The total funding for these research efforts was $2.79 million in 1982, $2.95 million in 1983, and is projected to be $2.95 million in 1984. (James T. Hall, Executive Secretary for USDA Research and Education Committee, personal communication, May 1983.)

The process, however, depends on a foundation of basic research. It appears that the public sector must provide leadership by laying the foundation for new crops. Historically, the development of the existing U.S. crops has depended on substantial Federal and State support; new crops will not be exceptions.*

New-crop development will depend on a certain amount of agronomic research carried out by ARS and State Agricultural Experiment Stations (SAES) and perhaps DOE (energy crops), Department of Defense (strategic crops), and Department of Commerce (marine plants). At the same time, however, funding for plant extracts work should be made available through competitive grants programs administered by USDA and other appropriate Government agencies. USDA is authorized under the Food and Agriculture Act of 1981 to conduct a competitive grants program on new crops. Not only is this an efficient way to match research needs with expertise but it reduces pressures within the agencies to maintain or increase traditional crops research at the expense of new-crop development.

Federal funding for new crops and plant extracts work is also available from NSF. NSF grants, however, generally are provided for basic scientific research, not for much needed applied research and development. For example, in the pharmaceutical area, funds are available for biochemical screening but rarely for follow-on research needed for drug development. NSF recently launched a new Small Business Grant program, but it specifically excludes grants for product development work. Bridging the gaps between basic and applied research and between research and product development is one of the major obstacles to new-crop development.

In addition to providing basic research and funding, the Government could be instrumental in stimulating private sector involvement in plant extracts by offering economic incentives for industry to invest in plant products. Given current economic conditions (e.g., recession, high-interest rates), a critical problem for the plant extracts industry will be how to leverage public and private funds for R&D so companies will be neither inappropriately subsidized nor discouraged from entering the industry. In addition to providing publicly funded "front-end" research, the Federal Government may need to provide other incentives such as tax benefits and low-interest loans to stimulate private interest in plant-extracts production. Such incentive systems must meet the needs of the companies, whether venture-capital firms, small businesses, or multinational corporations. Mechanisms available to the Government to encourage new-crop development and shifts in production should be examined.

One reason cited for industry's general disinterest in the plant extracts field, especially in plant-based pharmaceuticals, is uncertainties of patent protection. There seems to be some uncertainty about the patentability of different kinds of products and processes. In addition, some companies claim that they do not invest in natural-product development because it is difficult to obtain a product patent and because a processing patent, which is easier to obtain, does not offer sufficient protection against competitors. Industry also shows some hesitation to invest in research protected under a publicly owned patent. A risk exists that a competitor will use the Freedom of Information Act (FOIA) to obtain proprietary information on work done in an area protected by a public patent. Various agencies treat the FOIA differently; some will allow the sponsoring company to black out items of proprietary interest before information is made available; others will not. A related problem raises if a product or technique is developed in a State-supported institution; the sponsoring company cannot be given an exclusive license for it. The sponsor may be assured first right of refusal but the percentage return on sales must be negotiated, a time-consuming task that university scientists are apt to avoid. Another patent-related disincentive to industry's investment in plant extracts is specific to pharmaceutical companies. The length of a pharmaceutical patent (17 years) includes the time necessary for clinical testing, thus reducing the time the product is on the market and protected by the patent. Patent laws should be investigated in relation to plant extracts, and modifications to those laws to offer improved protection to companies investing in certain plant extracts work.

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*For more information see OTA technical memorandum, "Agricultural Postharvest Technology and Marketing Economics Research," April 1983.

In summary, potential Government roles in encouraging new plant-product development include the following:

1. provide SAES, ARS, or other Federal agency funding to nongovernment research bodies for R&D;
2. provide other incentives or eliminate disincentives in order to encourage private sector R&D;
3. carry out research itself in areas deliberately avoided by the private sector, when it is against the public interest to have research results protected by proprietary interest, and where public research would stimulate increased private investment; and
4. improve coordination of public research with the technical needs of industry.

Academia is a vital component of plant extracts work. Land-grant institutions provide expertise in agronomy and postharvest technology whereas other universities are relied on for advances in basic sciences (e.g., biochemistry, pharmacology, genetic engineering). While the public and private sectors depend on academic institutions for research advances, universities in turn rely on funding from public and private sectors. As a result of the intense international technological competition of the last half decade, many people feel that public research should be coordinated better with the technical needs of industry. One way to foster improved communication is through cooperative arrangements between industry and universities. Some such arrangements have been developed recently in the plant extracts area (e.g., General Foods Corp. and LPI for tobacco protein research, Procter and Gamble Co. and Oregon State University for cuphea research), but in general, the industry-academia link is strained by the question of proprietary interest. Research findings of universities are usually assumed to be available to the public. However, industry may be unwilling to support university research without some chance of long-term gain provided by proprietary rights to research findings. This raises concern about corporate influence on academic research topics and scholarly communication. While university scientists are concerned about limitations imposed by patenting, licensing, and need for secrecy about research findings, industry seems concerned over the lack of exclusive license for the product or process. In addition, some farmers have expressed opposition to funding by large corporations of agricultural research at universities for fear it will increase even further agroindustry's competitive advantage over small-farm operators or cutoff their access to much needed information. These limitations and conflicts must be resolved to facilitate industry-academia cooperation in plant extracts research.

Clearly, close cooperation is needed among Government, industry, and universities in new-crop development research to bridge the gaps between basic and applied (both agronomic and industrial) research. The respective roles of academia and the private and public sectors should be examined and public policy should be directed toward the goal of improving cooperation between universities and commercial enterprises.

Although each potential crop under investigation requires specific research, there are general research needs in new-crop and plant product development. A major constraint to selecting potential new crops is the unavailability of adequate field-screening techniques. Because plants cannot be screened in the field, large amounts of plant material must be brought in from the field to the laboratory for testing. Effective field-screening techniques would facilitate the discovery of new chemical compounds, new sources of known chemicals, and germ plasm for crop improvement and genetic engineering.

Research efforts involving chemical screening of plants often have been product- or activity-specific; the focus has been on finding particular chemicals or biological activities. For example, the National Cancer Institute's plant-screening program examined 35,000 plants for antitumor activity but made no systematic effort to record other biological activity observed. Plants tested by the program might not have exhibited antitumor activity but may have had other useful medical properties. Just as multiple-product development is cost effective, so is comprehensive screening. Improved communication and collaboration among research institutions would reduce duplication and encourage the development of advanced testing and screening technologies.

Crop Production

The needs and impacts of cultivating new crops, of course, depend on demand for the crop and the land area put into cultivation. Low-demand, high-price "specialty" crops such as the Madagascar periwinkle would require little acreage, so their impact on existing land-use patterns would be minimal. In contrast, new high-demand, high-volume crops such as hydrocarbon and leaf protein crops probably would have substantial impacts on the quantity and quality of national land resources. The following discussion refers to high-volume crops.

Land availability for new high-volume crops must be carefully assessed. Many such crops under study, including milkweed, jojoba, guayule, and crambe, are arid- or semiarid-land plants that thrive on lands marginal for traditional food and fiber crops. On these marginal lands, the decision to shift to a new crop will be largely an economic one and will be made as markets develop. Converting uncultivated arid and semiarid lands, both private and public, however, may be more difficult. Efforts to convert this land to effective cropland may well conflict with other uses such as grazing or recreation and involve complex property transfers.

While the decision of a farmer to shift production to a new crop is ultimately an economic one, the risk of allocating production resources to an unproven crop at first may seem too high. Even if farmers are assured regular markets for their products, initially they may need incentives to risk crop changes. Again, the Government could play a facilitating role in working closely with local bankers to ensure that long-term credit is available to farmers for new-crop production. Further, the Government might sponsor applied research on the crop to overcome farmers' resistance to it.

Assuming obstacles to allocating land for new-crop cultivation are overcome, effects on the quality of the land resources allocated to a new crop must be evaluated. Although some new crops would be better adapted ecologically to certain lands than traditional crops, any change in land use should be made carefully. Many arid and semiarid lands, for example, are highly susceptible to erosion, and unless the new crops are perennials and soil conservation techniques are implemented, erosion on previously uncultivated lands may degrade the land resource. New cropping patterns, such as multiple-cropping, may prevent such damage. Introducing a new crop may create pest and disease problems; new plants could introduce new pathogens or pests to an area or be susceptible to unforseen pest problems themselves. Many of the problems encountered with new-crop production are the same as those of traditional crops. But because new crops may change land-use patterns on marginal lands, which are more likely to be susceptible to ecological disruption, their impacts on the land base may be more pronounced.

Industrial Processing

The most serious technical constraints to new-crop development probably will occur at the product-processing stage. Processing technologies that appear feasible at the pilot level often encounter difficulties when scaled-up to commercial production. For example, although tobacco protein extraction seems technically promising at the pilot stage of development, technical problems with handling plant material, waste disposal, and solvent recovery are foreseen in commercial production. Commercial production also requires that plant capacity be fully used. Unless crop production is possible year-round, storage of the plant material will be necessary. When the quality of a major commercial plant chemical deteriorates rapidly after harvest (e.g., in leaf proteins, milkweed), processing must be coordinated with plant harvest.

Waste disposal, pollution, and other environmental effects from industrial processing represent another constraint on commercial production of plant extracts. Many extraction processes require the use of solvents. If these are not recycled, appropriate liquid-waste-management systems must be developed. Because waste water from processing for leaf protein and other plant extracts commonly has a high biological oxygen demand (BOD), it, too, could be a source of pollution if not disposed of carefully. Other environmental concerns associated with extraction are significant as well, and an economic assessment of plant extract technologies must factor in such costs.

There may be social costs involved when establishing processing and production facilities in areas previously economically depressed or in rural regions. Infrastructure needs, population shifts, inflation, and irregular boom and bust cycles of development are among the consequences of rapid economic growth. Planning for financing the front-end costs of development and for allocating resources within the community must be an integral part of large-scale commercial endeavors in plant extracts industries.

Marketing

Unless a market does or potentially can exist for a plant extract(s), industry probably will not invest in product development research and farmers will not invest in crop production. However, the development of a market *depends* on farmers' willingness to produce the crop and industry's willingness to invest in product research and marketing to stimulate product demand. This "Catch-22" of which comes first, the product or the market, exists for all new products but can be particularly complicated in the plant extracts field where agriculture and industry must be closely linked. The timing of markets is critical; marketing and crop production must be coordinated effectively. If markets are created before production can fulfill demand, buyers can become disinterested and the product's chance for success will be impaired. If production exceeds market demand, farmers will become disillusioned. Marketing a crop that has specialized uses and few alternative applications may be difficult because production must be closely coordinated with very specific markets. Production and processing of a multiproduct crop must be coordinated with many markets, which also may be difficult logistically.

Another marketing problem may arise if a market exists but well-established products already fulfill the demand. For example, tobacco protein (Fraction 1) would have to compete with egg albumin in the food processing sector and with alfalfa in the market for beta-carotene. Because both industries—egg albumin and beta-carotene—are well-established, tobacco probably would have a difficult time entering the market. Similarly, some of the products of milkweed (pectin, fiber, livestock feed) would have to compete in the marketplace with well-established domestic sources of these goods.

All new crops would need agronomic refining and new products need processing improvements after scale-up to commercial production. In order for farmers and industrial producers to invest in the crop, however, it would have to be profitable or perceived to have commercial potential even before refinements have been made. One way to overcome this barrier would be to introduce a product from the crop as a "specialty item." This high-priced item could make the crop competitive in the short run with traditional crops and could act to encourage the crop's expanded development. The crop could be grown in small quantities for predictable returns, thus enabling farmers to solve production problems and providing the time necessary for further agronomic and processing research essential for long-term development of the crop. This leveraging method is being employed with jojoba. Small-scale commercial production of the plant is supported by commercial sale in health food specialty markets (e.g., shampoos, skin creams). Once crop and product production methods are refined, jojoba can be cultivated on a much larger scale for its potential high-demand oil.

Consumer acceptance of the product(s) is, of course, the most important factor in marketing success, and sometimes the most unpredictable. Soybean meal has been developed and produced as a high-quality, low-cost source of protein for human consumption, but consumers prefer to buy other more expensive proteins. Tobacco leaf protein faces a similar obstacle. Although technical problems remain, the LPI process could be scaled-up to commercial production at this time. The overriding deterrent to commercial production, however, is producers' lack of confidence that consumers would accept tobacco protein concentrates as protein supplements or cigarettes produced from deproteinized tobacco.

In summary, constraints to new-crop development are many and need to be overcome from beginning research to final marketing. Such constraints in research, crop production, industrial processing, and marketing include:

- research:
  - insufficient cooperation among the Federal Government, States, universities, and industry;
  - scant research dollars identified for such research;
  - inadequate linkages between basic and applied research and product development;
  - lack of Federal economic incentives to increase industry's involvement;
  - inadequate field-screening techniques.
- crop production:
  - possible major changes in current land-use patterns;
  - lack of incentives for farmers to take risks with new crops;
  - potential adverse environmental impacts of some new crops on the natural resource base;
- industrial processing:
  - the difficulties in scaling-up from pilot operations to full-scale production;
  - waste-disposal problems faced at full-scale commercial production;
- marketing:
  - the "Catch 22" of which comes first—the product or the market?;
  - breaking into the market that is already filled by established products;
  - developing consumer acceptance of new products.

AREAS FOR POSSIBLE CONGRESSIONAL ACTION

The potential for the technological and scientific screening of plants to find the new useful substances they contain has barely been tapped. Research to date strongly suggests that this is a promising field that could provide wide-ranging benefits to the United States in the near and far term, especially if nonrenewable fossil fuel resources climb in cost. To date, no more than an estimated 10 percent of the world's 500,000 to 750,000 higher plant species have been screened for their chemical makeup even in a cursory manner. Nevertheless, the array of useful and important products extracted from plants is impressive.

Today, a worldwide concern exists among scientists that plant materials as yet unscreened are being lost before their potential value is determined. Loss of genetic plant materials probably is greatest in the Tropics where pressures to clear vegetated land for agriculture to feed rapidly growing populations are extremely heavy. (See OTA report entitled *Technologies To Sustain Tropical Forest Resources.*)

Discussions of the experts assembled by OTA reflected a need for the United States to address the issues and problems above in a timely fashion. Because of the rate of land-clearing worldwide, society may no longer be able to afford the luxury of postponing action to some far distant date. Three opportunities for possible congressional action emerged from this exploratory activity:

- develop a coordinated, comprehensive plan involving the Government, industry, and universities to screen plants, assess new chemical resources from the plants, and foster their commercial development;

- assure adequate funding for Government, university, and industry research into plant screening for the extraction of commercially valuable substances and for crop and product development;
- provide incentives (e.g., tax benefits, subsidies) or minimize disincentives (e.g., uncertainties in patent laws) so as to encourage research by industry on new crops for chemical extracts; and
- encourage bilateral and multilateral agreements for cooperative research and evaluation of untested species.

No coordinated, comprehensive U.S. plan involving the Government, industry, and universities exists for: 1) screening U.S. or foreign plants for their natural chemical components, 2) determining the nature and possible uses for the natural plant chemicals they may contain, and 3) fostering development of such new crops and their commercialization. Scattered efforts are under way in the United States to deal with some of these needs but the total effort is small. Traditional major food and fiber crops have strong agricultural lobbies behind them that work hard to maintain Federal and State Government attention and research. Potential new crops and chemical-screening efforts lack the support of similar strong lobbies. Industry generally focuses on deriving benefits from their research over the short term. It is unlikely, therefore, that they would undertake a broad-based, long-term analysis of the thousands of plants as yet unstudied. In addition, vertically integrated, very large food industries concentrate mostly on food processing and generally rely on others to conduct basic research on new crops and new products.

Adequate funding is lacking for R&D in plant screening for chemicals and for development of new crops bearing such chemicals. Competition for current funds is keen. Unstudied plants have no markets or products when they are first investigated, and even with research it is not certain that the plant will yield useful products. Should new products be developed, markets for them may not exist, or if they do exist the market demands already may be being met by other materials from different sources. The history of agriculture shows that the major U.S. crops have depended heavily on large Government expenditures for research, development, and farm subsidies. The development of a new crop in the past has not and probably cannot now depend solely on the efforts and funding of the private sector. Bringing new crops into the marketplace usually requires a long period of time. During this time of R&D the commitment for continuity of support is key to maintaining industry's interest. The private sector is unlikely to be willing to pay all costs for developing a plant product or risk working on the crop at all unless assured that a continuing commitment to the crop's research and development exists. It seems likely that Federal support in the form of Government research and funding for private research will be required to move crop or product development along to a point where the private sector ultimately can take over.

In addition to its role in carrying out or funding research, the public sector has a role in providing incentives or minimizing disincentives in order to stimulate private sector interest in commercial development of plant chemicals. Such incentives might include tax benefits or other forms of subsidies for farmers and industries developing new crops and plant products. Disincentives to industry's participation in this area include uncertainties in patent laws. Some industries seem to feel that existing product or processing patents offer insufficient protection against competitors. There also seems to be some confusion about the patentability of plant material. Although university-industry cooperation represents an advantageous meshing of expertise and funding, industry often hesitates to enter into such arrangements for fear of insufficient control over research results. For the same reason industry may hesitate to engage in research protected under a publicly owned patent, protection of key research findings cannot be assured. OTA workshop participants expressed a concern over perceived problems arising from patent law. They see a need for the Government to examine certain patent laws as they apply to plant-extract industries and, where appropriate, change these laws to provide adequate incentives to industry to invest in plant-chemicals research.

Clearly, if the potential for commercial development of plant chemicals is to be exploited, R&D in this field needs to be coordinated among Government, academia, and industry.* In light of increased concern over rapid loss of genetic plant material worldwide, increased action in this area seems appropriate now. The role of Congress could include the following actions:

1. Congress could request an evaluation of the status of science and technology related to extracting chemicals from plants and the development of associated new crops. The study would assess at least the following three issues:
   - basis for a coordinated plan for commercial production of plant extracts and developing associated new crops;
   - funding requirements for long-term R&D;
   - incentives and patent-law uncertainties that might be a disincentive for industry involvement.

   The study could examine and assess the major constraints to and opportunities for establishing new industries that could extract important chemicals, medicines, and protein, for example, and develop associated new crops. It could assess ways to minimize the constraints and to analyze potential impacts of taking such actions.

   The study could outline possible ways to establish a mechanism for Congress to obtain continuing information and advice on plant-chemical industries and associated new crops, research priorities, and methods for improving coordination among Government, industry, and academia.
2. Congress could hold a series of hearings to address such issues as:
   - the need for a coordinated plan for R&D of plant extracts and associated new-crop development;
   - the needs for R&D funding;
   - incentives and patent-law uncertainties that might be a disincentive for industry involvement; and
   - consideration for the establishment of a "plant extracts/new crops advisory council" comprised of members of Government, academia, and industry.

   Participating committees could be those having jurisdiction over such topics as agriculture, science and technology, commerce, marine environment, international development, medicine, strategic stockpiles, and public health.
3. Upon completion of such hearings, Congress could, if the need is justified, take appropriate actions to form a permanent "plant extracts/new crops advisory council."

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*One attempt at coordinating research and development on new crops is contained in Public Law 95-592, Native Latex Commercialization and Economic Development Act of 1978. In the act, a Federal agency coordinating commission was established to oversee R&D work on Guayule. In 1983, the commission membership and scope were broadened under H.R. 2733, Critical Agricultural Materials Act. As of this writing, the bill has passed the House and full Senate action is pending.

Appendix

Technical Papers

AN ALTERNATE USE FOR TOBACCO AGRICULTURE: PROTEINS FOR FOOD PLUS A SAFER SMOKING MATERIAL

Samuel Wildman
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Abstract

Tobacco could be developed as an important food crop in combination with its traditional use for smoking and chewing. As a food crop, tobacco grown in dense spacing could produce about four times more protein per acre than soybeans and about five times more dry tobacco for smoking than conventional tobacco crops. A simple method has been developed for extracting the proteins from the aerial portions of fresh tobacco and other plants. The water soluble proteins have unique nutritional and functional properties that could make them valuable for the package food industry and for medical use. The insoluble proteins have properties similar to soy protein. A byproduct of growing tobacco for food proteins is a deproteinized smoking tobacco that has lower concentrations of chemical compounds known or suspected to have adverse effects on cigarette smokers.

Plant, Extraction Products, and Extraction Techniques

Plant

Ninety-nine percent of the tobacco used for smoking and chewing is obtained from *Nicotiana tabacum*. This plant was a weed believed to have been domesticated in Latin America long before Columbus' discovery of the New World. Today tobacco is grown on every continent except Antarctica, and is found in both hemispheres at latitudes from the Equator to 55°. World demand for tobacco is enormous and, despite smoking's adverse effects on health, the demand continues to grow. At least 4 trillion cigarettes were consumed in 1981. About 2.5 million hectares (6.2 million acres) of land worldwide are devoted to tobacco plants that are used exclusively for smoking and chewing China uses nearly a million hectares for growing tobacco, and the United States nearly 400,000 hectares, followed by smaller areas in nearly every other country in the world.

Some people believe that the future of tobacco is in jeopardy, at least in Western countries where per capita tobacco consumption is declining. Tobacco is being attacked increasingly by health authorities, as medical evidence accumulates on the adverse effects of smoking on health. However, this situation could change because a simple process that extracts high-grade proteins suitable for human consumption from tobacco plants has been developed (9). A byproduct of the extraction process is a deproteinized cigarette tobacco (10) considerably reduced in components hazardous to smokers' health.

Potential Uses of Major Extraction Products

The extraction process perfected to a pilot plant stage by Leaf Proteins, Inc. (LPI) yields the following six potentially useful products.

1. **Crystalline Fraction 1 protein.** This product constitutes more than 30 percent of the total protein in tobacco leaves. It is soluble in water, is tasteless and odorless, and is composed entirely of amino acids of high nutritional quality. When fed to rats, crystalline Fraction 1 protein exhibited a somewhat higher protein efficiency ratio (PER) than casein, the standard commonly used for comparing the nutritional quality of proteins (4).

Crystalline Fraction 1 protein has unique properties that might be used in medicine. When washed free of sodium and potassium, the crystals might be used in patients with kidney failure to meet their amino acid requirement without taxing the kidney's inability to eliminate cations. Crystalline Fraction 1 might also be used to meet the entire protein requirement of patients with acute gastrointestinal problems or patients recovering from surgery of the alimentary canal. The amino acid mixtures used in patients with kidney disease are expensive and they taste, at best, vile. Since crystalline Fraction 1 protein is tasteless, it could be incorporated into appetizing diets and is potentially more economical than amino acid mixtures now used.

Properties of crystalline Fraction 1 protein render it potentially useful to the package food industry. Because it is tasteless and odorless, it could be added to food without altering the food's taste and smell. As a dry, almost white powder, it could be mixed with cereal grains to improve their protein content and quality. It might be used as a milk substitute in countries that lack a dairy industry. In its soluble form, it could be added to soft drinks, removing them from the junk food category. Similar to egg albumin, Fraction 1 protein irreversibly gels when heated above 80° C (176° F). Its functional properties, such as "heat set," are similar to egg albumin or casein that are widely used throughout the package food industry. The amino acid composition, protein efficiency ratio (PER) data, and data concerning functionality properties of Fraction 1 protein are given in appendix 1.

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*Retired, Leaf Protein International, Inc.

2. **Fraction 2 protein.** This product also is water-soluble and of high nutritional value. Its main use could be as a supplement to upgrade the nutritional quality of cereals and other food products. The functional properties of Fraction 2 protein are less desirable than those of Fraction 1 protein, but improvements in extraction procedures may eliminate this difference. The amino acid composition of Fraction 2 protein is shown in appendix 2.

3. **Green sludge.** This product consists mainly of water insoluble proteins and starch. Because it also contains beta carotene and xanthophyll, green sludge could be marketed as a supplemental feed for poultry and monogastric animals. By solvent extraction, green sludge can be converted into a material similar in properties and amino acid composition to defatted soybean meal. The decolorized material could be used in the food industry for the same purposes as soybean meal. The essential amino acid compositions of green sludge protein and of soyflour protein are compared in appendix 3.

4. **Green residue.** This product is a fibrous material whose solids are composed of more than 50 percent cellulose and hemicellulose and about 13 percent protein. Its nutritional value is similar to that of alfalfa hay. By solvent extraction, green residue is dehydrated and converted into white fibers that can be used for manufacturing deproteinized cigarette tobacco. The chemical composition of dried green residue and a comparison of the composition of white fibers and wheat bran are given in appendix 4.

5. **Pigments and other bio-organic compounds.** These are products of organic solvent extraction of green residue and green sludge. The material can be separated further into chlorophyll, carotenes and carotenoids, solanesol, and other compounds of lipoidal nature. Poultry producers use large quantities of purified carotenoids.

6. **Low molecular weight compounds.** This product is composed of water soluble sugars, amino acids, vitamins, salts, and other compounds. When concentrated by evaporation of water to about 10 percent solids, the product probably could be used as a fermentation liquor. The product is used as a flavoring and coloring material which, when added to the white fibers, produces a deproteinized cigarette tobacco low in components thought to be harmful to health. The apparent tar and nicotine composition of LPI deproteinized tobacco and conventional cigarette tobacco are compared in appendix 5.

Processing Technique

Operation of a pilot plant in North Carolina during 1981 and 1982 demonstrated the commercial feasibility of the LPI process for obtaining crystalline Fraction 1 protein and the other raw materials from tobacco. The processing technique is diagrammed in figure 1. There are six steps of the LPI process as described below.

1. **Disintegration of plants.** The aerial portions of fresh tobacco plants are placed on a conveyor (fig. 2) for transport to the mouth of a Rietz Disin-

Figure 1.—Schematic of the LPI Process for Obtaining Proteins and Other Products From Tobacco and Other Plants

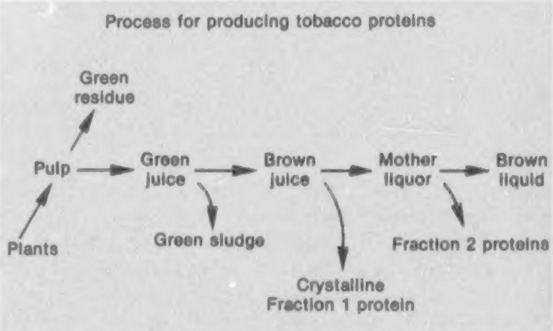
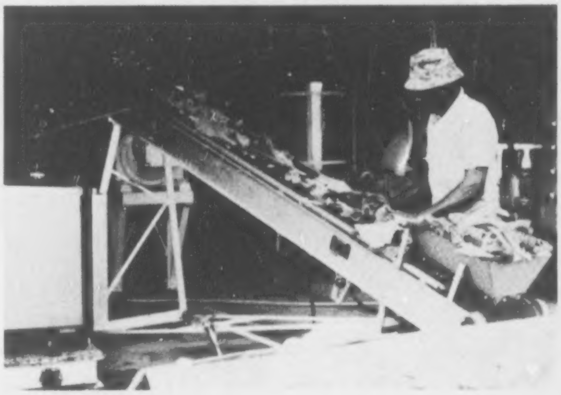


Figure 2.—Conveyor Transporting About 15 lb of Tobacco Plants per Minute at Beginning of LPI Process

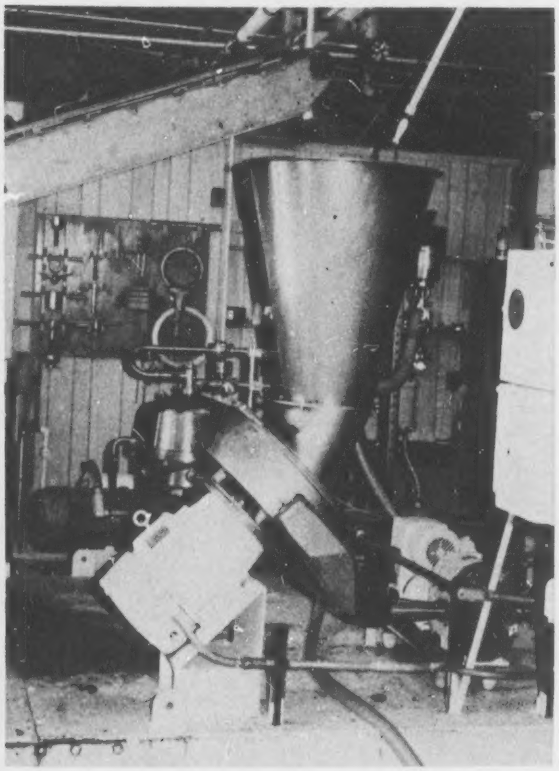


tegrator (fig. 3), where the plants are sprayed with a 0.5 percent solution of sodium metabisulfite in water as they fall into the pulping device. Sodium metabisulfite, listed as GRAS, is used widely in the food industry. It is the only exogenous chemical added during the extraction process.

2. **Extraction of green juice from disintegrated plants.** The pulp emerging from the disintegrator is pumped into a Rietz Rotary Press (fig. 4) where pressure from a mechanical screw forces out a green juice through a fine-mesh screen while retaining the green residue until it is discharged into a wheelbarrow (fig. 5) at the other end of the press.

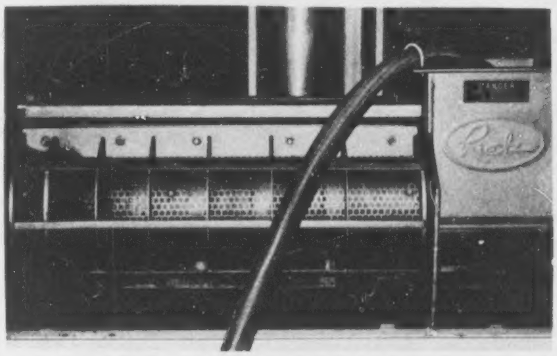
3. **Removal of green sludge from green juice.** The green juice emerging from the press is pumped through a heat exchanger so that the juice is heated rapidly to about 125° F, then cooled rapidly to room temperature. The abrupt temperature change aids in particulate matter aggregation to which the green pigments and other lipoidal compounds are attached. The juice then enters a Westphalia SB-7 Continuous Flow Centrifuge (fig. 6) which removes all of the starch and about 85 percent of the green particulate material which is discharged periodically as green sludge (fig. 7). A partially clarified brown juice emerges from the centrifuge.

Figure 3.—Plants Falling Off Conveyor Into Mouth of a Rietz Disintegrator



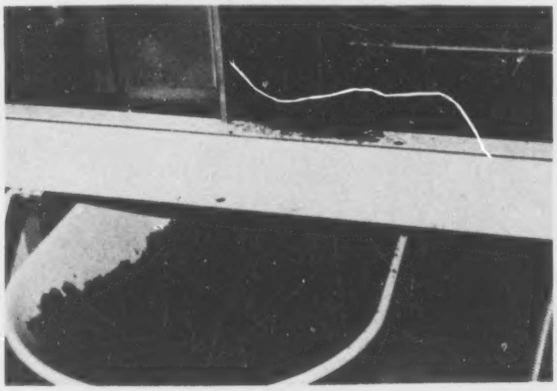
White pipe at 60° angle at top right is fitted with a nozzle to spray plants with 0.5 percent sodium metabisulfite solution as they pass into pulping chamber. Pulp is pumped (lower right) to the press shown in figure 4

Figure 4.—Hose Containing Pulp Being Conveyed to Opening of a Rietz Rotary Press



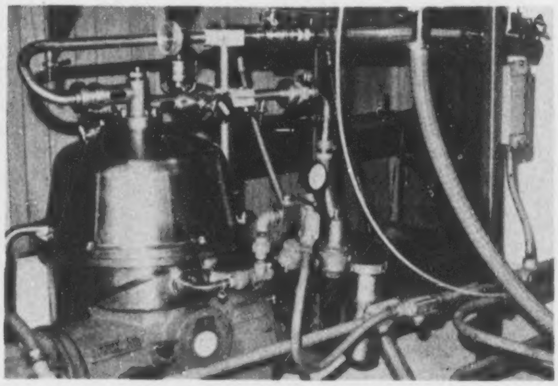
Green juice is squeezed out through fine-mesh, stainless steel screen in center of press and drips into sump beneath. Green residue is forced by rotating screw to left end of press for discharge

Figure 5.—Wheelbarrow Located Beneath Press To Catch Discharged Green Residue With Moisture Content of About 65 Percent



4. **Filtration of brown juice.** The partially clarified brown juice containing soluble proteins is pumped to a Rotary Vacuum Filter (fig. 8) whose filter is made out of diatomaceous earth. The filter removes the last traces of green sludge. The clear brown juice (fig. 9) emerging from the filter (fig. 10) is sent to a storage tank where crystallization of

Figure 6.—Westphalia Disk Type Centrifuge



Used to remove about 85 percent of green sludge from green juice coming from press and after having been heated momentarily to 150° F and cooled to ambient temperature on the way. Green juice enters centrifuge at top and exits via plastic hose partially hidden by dial (center of photo) on way to rotary press shown in figure 7

Figure 7.—Green Sludge After Discharge From Centrifuge

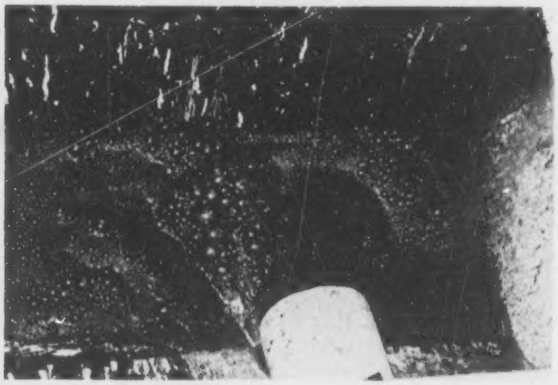
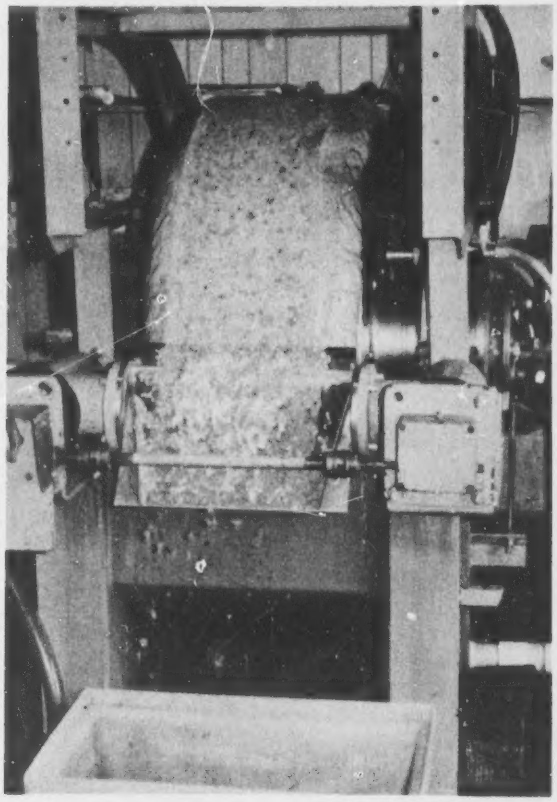


Figure 8.—Rotary Vacuum Filter Whose Surface Is Covered by a Thick Layer of Diatomaceous Earth Which Dips into a Reservoir of Plant Juice (obscured in photo) as It Rotates



Green sludge not previously removed by centrifuge in figure 6 is caught on surface of filter while brown juice containing soluble proteins is sucked through the pores of the filter cake by the vacuum. Green sludge "blinds" the filter so that the surface must be constantly renewed by the knife seen removing very thin layer of filter cake so that a renewed filter surface reenters the reservoir of plant juice at bottom of filter

Fraction 1 protein begins within 3 to 6 hours of storage and is completed within 3 to 4 hours after the first crystals appear. If left undisturbed, the crystals will settle into a layer at the bottom of the vessel.

5. **Collecting and washing Fraction 1 protein crystals.** Because funding limitations have precluded purchase of equipment for a more efficient washing method, the crystals are collected by passage through the SB-7 centrifuge and the mother liquor is sent to a storage tank. The crystals are resuspended in tap water followed by recentrifugation and a second washing cycle. After the crystals are discharged from the centrifuge and allowed to settle, they compact into a nearly colorless suspension of about 10 percent protein in water (fig. 11).

6. **Collecting and washing Fraction 2 protein.** While not a desirable method because of denaturation of proteins, limited resources necessitated adding acid to the mother liquor to precipitate the Fraction 2 proteins at pH 4. The Fraction 2 protein precipitate is collected by centrifugation, and the brown liquid containing the low molecular weight compounds is sent to a storage tank. The precipitate then is resuspended in water and washed in the same manner as the Fraction 1 protein crystals.

Figure 9.—Brown Juice Coming From Rotary Vacuum Filter at About 4 L/min (1 gal/min) Entering Storage Tank Where Crystallization of Fraction 1 Protein Will Occur

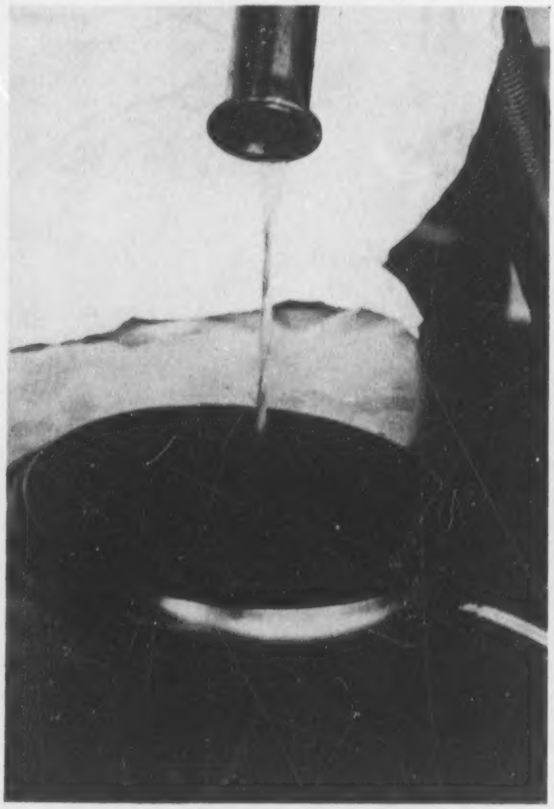
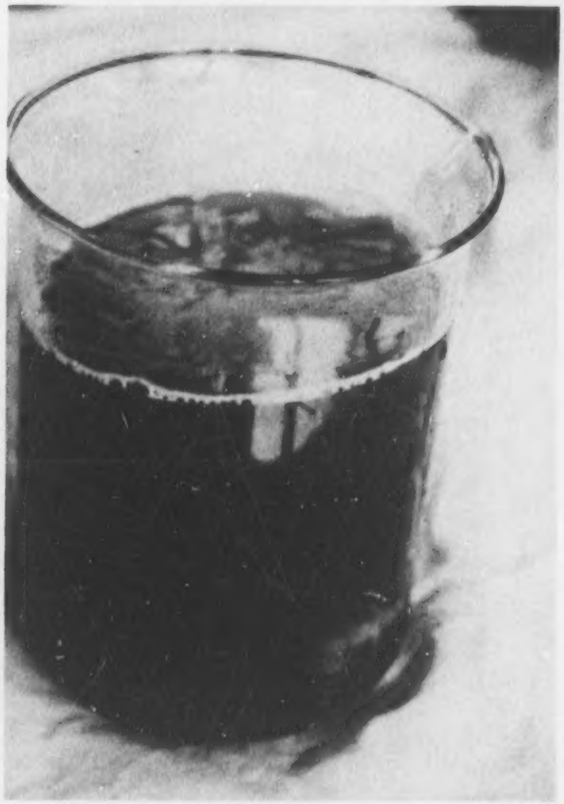


Figure 10.—Appearance of Brown Juice Before Crystallization of Fraction 1 Protein Has Occurred Showing It To Be Devoid of Green Sludge

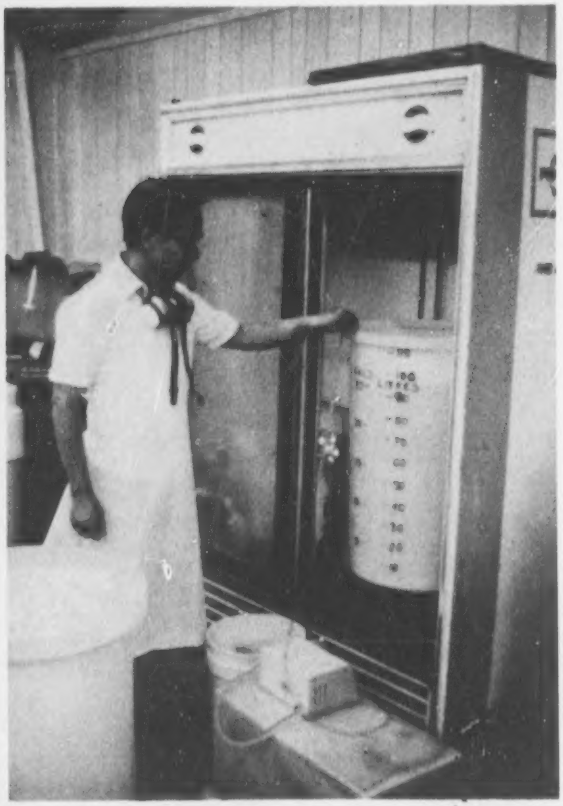


Level of Development of Technology

LPI, a California corporation, developed and patented its simple method for obtaining crystalline Fraction 1 protein and developed and patented a method for converting green residue into a deproteinized tobacco suitable for cigarettes. To explore the commercial possibilities of the protein extraction process, LPI formed a joint venture with the North Carolina Farm Bureau Federation which, together with General Foods Corp., provided funds and equipment to construct a pilot plant at Lucama, N.C., in the heart of the flue-cured tobacco region. The pilot plant was operated for the first time in August 1980, but was unable to produce Fraction 1 protein of desired purity during the remaining 2 months of the growing season. The following summer, acceptable Fraction 1 protein was made in a few experiments, but unusual drought conditions destroyed much of the plant material designated for the pilot plant program. Each experiment required a minimum of 600 lbs (272 kg) of fresh plants. Not until July 1982 could the pilot plant consistently produce crystalline Fraction 1 protein of high purity. As of September 1982, the pilot plant has operated without failure on 14 occasions to produce Fraction 1 protein crystals. The plants used in these experiments were harvested from various fields, at various stages of growth, and after exposure to various climatic conditions. The success of the pilot plant operations conducted during 1982 demonstrates the feasibility of the LPI process as a method of producing pure Fraction 1 protein and its byproducts on a commercial scale.

The existing pilot plant is capable of processing about 1 gallon (3.785 l) of plant juice per minute or about 1 ton of fresh tobacco plants during a 6-hour run. After 6 hours, the process flow must be interrupted for 3 to 4 hours to clean up and remake the

Figure 11.—Appearance of a Suspension of Washed Fraction 1 Protein Crystals



Crystals obtained by processing about 1 ton of tobacco plants by the LPI process. Crystals have settled below the 60 L mark on the vessel, the layer of crystals consisting of about 10 percent Fraction 1 protein (dry basis)

filter cake. With another rotary filter, the pilot plant could be operated continuously. With larger capacity filters, the process rate could be doubled or tripled without changing the other equipment. With a larger capacity disintegrator, the process could handle 5 gallons (19 l) of juice per minute.

According to laboratory determination, the yield of raw products from 1,000 kg of fresh tobacco plants is as follows:

- 20 kg of Fraction 1 protein crystals (80 percent water);
- 10 kg of Fraction 2 protein precipitate (80 percent water);
- 250 kg green residue (64 percent water) containing raw material for cigarette tobacco;
- 100 kg ton green sludge (70 percent water) containing insoluble proteins and starch; and
- 1,060 l (280 gal) of brown liquid containing 2 percent low molecular weight, water soluble, solids.

Wet Fraction 1 protein crystals were shipped to a custom, spray-drying company which found that spray-drying produced a powder of Fraction 1 protein that was stable at room temperature. The powder readily dissolved in water to produce a Fraction 1 protein solution with properties equivalent to those before drying.

Table 1 shows the expected yield of dry Fraction 1 protein and its finished byproducts per 60 tons of fresh tobacco. This is the average biomass of closely grown tobacco plants expected per acre per growing season in a climate like that of North Carolina. The figures in column 3 of table 1 are based on existing pilot plant yields, but for realization would require additional spray-drying capacity of 1.3 gal/hr (4.9 l/hr), water evaporation capacity of

Table 1.—Yield and Estimated Value of Finished Products From Tobacco

Finished product	Minimum estimate of wholesale value	At 60 ton plant/acre/growing season: Yield (dry)	At 60 ton plant/acre/growing season: Value
White fibers for cigarette tobacco	30¢/lb	5.3 ton	$3,500
Decolorized insoluble protein + starch (equivalent to soybean meal)	$150/ton	1.8 ton	290
Carotenoids for poultry	$7/oz (25¢/gram)	13.2 lb (6 kg)	1,500
Fraction 1 protein (equivalent to egg white)	$1.81/lb ($4/kg)	529 lb (240 kg)	960
Fraction 2 protein (equivalent to soy protein)	45¢/lb ($1/kg)	265 lb (120 kg)	120
Condensed brown liquid	No estimate	1.4 ton	No estimate
			$6,370/acre

13 gal/hr, and organic solvent extraction and recovery capacity of 5.3 gal/min. Column 4 shows the estimated dollar value of the products based on the minimum estimate of wholesale value in column 2.

State of Art; Additional Research and Development

As mentioned earlier, the SB-7 centrifuge was used for collecting and washing Fraction 1 protein crystals. Preliminary studies indicate that washing Fraction 1 protein crystals by ultrafiltration or reverse osmosis could be more efficient. Additional comparative experiments need to be made before deciding on which equipment to install for continuous operation.

Preliminary experiments on a laboratory scale suggest the possible advantage of simultaneous concentration and washing of Fraction 2 protein by ultrafiltration, a procedure that would avoid the denaturation now caused by acid precipitation. Further experiments are needed before deciding on the best equipment to install for continuous production of the Fraction 2 protein product.

More work needs to be done on solvent extraction of green residue and green sludge and on methods for recovering the solvent and refining the carotenoids and other compounds extracted by the organic solvent. Preliminary work need not be on a scale to keep up with the green juice process stream, but should be at a level sufficient to produce 5 to 10 lb batches of white fibers needed for evaluation by tobacco manufacturers.

Other Sources of the Extraction Product

About 40 years ago, N. W. Pirie (8) of England advanced the idea of using leaf proteins for human food and developed a technology for extracting them from various plant species. While nutritious, the protein preparations were green colored and had an odor, taste, and texture that made them largely unacceptable to the human palate.

1. **Pro-Xan process for obtaining alfalfa proteins.** A group at the USDA Western Regional Research Laboratory under the leadership of Dr. G. O. Kohler modified and enlarged the Pirie process to where 10 tons/day of alfalfa leaf protein known as "Pro-Xan" could be produced for animal feed (5). A plant of this capacity consumed 40 tons/hr of green chopped alfalfa. In 1977, the cost of such a plant was estimated by USDA to be $3,334,477 (3). The annual operating cost, for 22 hr/day and 130 days/yr, was estimated to be $401,796. Field chopped alfalfa is treated with ammonia while being crushed to express a green plant juice whose proteins then are coagulated by heat. When dried, the green Pro-Xan contains 57 percent protein, 9 percent lipoidal material, and 100 mg xanthophyll per kg. Xanthophyll, a yellow pigment, is valuable for the color it imparts to chicken flesh and egg yolks. Industrial plants were in operation until the market for dehydrated alfalfa disappeared in the United States. A Pro-Xan II process evolved to the pilot plant stage whereby a Pro-Xan type of product containing less protein and more lipid was removed before the remaining soluble proteins were coagulated by heat to produce, when dry, a bland, off-white material containing 90 percent protein (2). The off-white protein was greatly improved in the organoleptic properties that prevented acceptance of the original Pro-Xan by humans. Table 2 shows some of the differences in quality of the products produced by the Pro-Xan II process from alfalfa compared with the products produced by the LPI process from tobacco.

2. **LPI process for alfalfa and other plants.** The products enumerated in table 1 have also been obtained on a laboratory scale by the LPI process from the aerial portions of alfalfa, soybean, clover, and

Table 2.—Quality of Products Obtained From Alfalfa Plants by the Pro-Xan II Process Compared With Those From Tobacco Plants by the LPI Process

Product	Alfalfa	Tobacco
Green residue	Can be used only for animal feed	Used for deproteinized cigarette tobacco and for animal feed
Green sludge	Same as tobacco	Same as alfalfa
Fraction 1 protein	Denatured together with Fraction 2 protein to yield water insoluble material containing 90% protein	Obtained as crystals containing more than 99% protein which redissolves in water
	2% of total solids	4% of total solids
	No functionality	Functional properties similar to egg white
	Some taste and color	Odorless and tasteless
Fraction 2 protein	Denatured and mixed with Fraction 1 protein	Contains no Fraction 1 protein
		2% of total solids

sugar beets, and probably could be obtained from other plants with succulent leaves such as cotton, tomato, eggplant, spinach, etc.

3. **USDA method for obtaining tobacco proteins as byproducts of the homogenized leaf curing process.** USDA has been developing a process known as homogenized leaf curing (HLC) that was conceived by Dr. T. C. T'so and associates as a means to provide a simplified industrial method for producing safer tobacco. Donald De Jong and Jesse Lam, Jr. (1) set up a pilot plant at Oxford, N.C., for recovering edible proteins from the plant juice released during the pulping process at the beginning of the HLC process. After squeezing the green juice from the residue, green sludge is removed from the juice by centrifugation. The soluble proteins then are precipitated by acid and the deproteinized liquid is added back to the green juice. The mixture is allowed to incubate at ambient temperature before being dried and made into deproteinized, reconstituted tobacco sheet for cigarette manufacture. The acid coagulated proteins are less valuable than crystalline Fraction 1 protein from tobacco because acid denaturation destroys the functional properties of the protein. However, it would be relatively simple to modify the Oxford pilot plant to produce crystalline Fraction 1 protein by the LPI process.

Use of Technology

LPI was founded in 1979 with the goal of transforming tobacco into a commodity used on a large scale for human food as well as for smoking. Private capital supported the pilot plant operation. A great opportunity exists for the private sector to participate in developing the pilot plant process into a profitable commercial venture. The possible role for government is twofold. First, it could have a short-term role in providing financial aid to perfect the process so that large enough quantities of the products can be made for long-term animal feeding tests. These tests are needed to obtain FDA approval before Fraction 1, Fraction 2, and the insoluble proteins can be marketed for human consumption. Second, government could support testing of the health effects of deproteinized tobacco relative to conventional tobacco. If deproteinized tobacco prepared by the LPI process is less hazardous, governmental involvement with this product is justified by national health considerations.

Agronomic Considerations and Requirements

Agricultural Scales and Systems

1. **Biomass in relation to protein yield.** The agronomic factors that affect smoking quality and now determine the value of conventional tobacco are not so important when tobacco plants are to be used for proteins and deproteinized tobacco. During processing of the green residue into reconstituted cigarette tobacco, flavorants can be added to make the product acceptable to smokers. Thus, the most important agronomic factor affecting commercial development of the LPI process will be maximizing production of plant biomass per unit of land per growing season at minimum cost.

Production of biomass is a direct function of photosynthesis. The amount of photosynthesis is related to the total area of green leaves exposed to the sun (7). When the bottom leaves are shaded from sun and turn yellow, the photosynthate accumulated in the form of starch, proteins, sugars, and other compounds is destroyed in a secondary process of supplying nutrients to the roots and topmost portion of the plant where rapid growth is occurring. A balance is reached where further growth in the biomass will not increase the protein yield per unit of biomass. This balance exists when the canopy of plant leaves completely covers the ground and the plants have grown until the leaves nearest the ground start to turn yellow. At this point, the plants should be harvested and processed for maximum yield of proteins.

2. **Multiple harvests of densely spaced plants.** Tobacco has tiny seeds, so plantlets arising from seeds also are small and vulnerable at the beginning of the growth period. With ideal conditions of moisture, soil fertility, temperature, duration of sunshine, and freedom from insect and parasite attack, in 5 to 6 weeks the seedling could grow to a height of 18 to 20 inches with its leaves covering an area of 1 square foot or more. Under these conditions, a planting density of 44,000 plants per acre would produce a closed canopy 5 to 6 weeks after seeding. Periods of drought, inclement weather, etc. would lengthen the time until the canopy is closed. One or two weeks of additional growth after the canopy closes brings the biomass to the balance point at which it should be harvested.

During harvest when the stalks of tobacco plants are cut off about 4 inches above the ground, each stalk will regenerate two to three new aerial shoots. If soil fertility and moisture are maintained, the new shoots will grow rapidly and form new leaves, soon growing to a size close to that of the previously harvested shoot. The leaf canopy of closely spaced plants with regenerated shoots will close in about 5 weeks, so that a second harvest of biomass can be made about 6 weeks after the first harvest. By this process of "rattooning," four biomass harvests have been obtained from the same plants in the 5-month growing season in North Carolina. The appearance of densely grown plants ready for a first harvest in early June 1982 is shown in figure 12.

3. **Dense spacing by transplanting.** Because of their small size, tobacco seeds are usually germinated in plastic-covered seed beds whose soil has been fumigated with methyl bromide to eliminate diseases and, most importantly, to prevent weeds from germinating and crowding out the smaller tobacco plants. The tobacco seeds are sown at a density of about 100 seeds per square foot, and about 2 months after germination are ready for transplanting. With existing farm equipment, transplants for protein production could be spaced at about 30,000 plants per acre so that closing the canopy might require 7 to 8 weeks with a similar time interval between rattoon harvests.

4. **Close-spacing by direct sowing of seeds.** It is likely that the need for transplanting can be avoided in growing tobacco for protein production. For example, each year S. P. Willingham of Florida grows 160 acres of directly seeded, closely spaced tobacco seedlings, which he sells for transplants to other tobacco farmers. To avoid fumigation he clears new palmetto scrubland each year and prepares the soil in 6-foot-wide beds raised 6 to 8 inches above the surrounding soil. The region is frost-free and irrigation keeps the small plantlets moist during their vulnerable period immediately after germination. There is no need to cover the beds with plastic. Even when sown in the cool period during the last week of December, in 60 days the plants will have grown to harvestable size for protein production. The disadvantage of the system is the requirement for new land each year.

Figure 12.—Close-Grown Tobacco Plants in North Carolina Ready for a First Harvest for Protein and Deproteinized Tobacco in June 1982

Chemical growth retardants that kill grass-like plants without harming tobacco are available. Experiments in Florida and North Carolina indicate that directly sown tobacco seeds could be grown in dense spacing on a raised bed system such as Willingham's. Weed control would be accomplished by proper cultivation of the soil prior to sowing and by use of selective growth retardants after germination of tobacco seeds. As in Florida, success of the system would depend on a reliable irrigation system.

Tobacco seed can be pelleted, making it possible to sow the seed in rows. Curtis Griffin of Florida has developed machinery that could be modified to sow seed in dense spacing within a row.

5. **Cultivars of tobacco.** Conventional tobacco agriculture uses the species *Nicotiana tabacum* almost exclusively. Different cultivars of *N. tabacum* are used to obtain desirable flavor or other qualities. Examples are the NC 95 cultivar grown extensively in the flue-cured region of North Carolina and the KY 14 cultivar grown in the burley producing States. Cultivars not in use now may prove more desirable for protein and deproteinized tobacco production. Some cultivars produce less than 10 percent of the nicotine ordinarily found in tobacco. Other cultivars do not produce flowers until late in the growing season, which could increase the biomass yield. Professor R. C. Long, of the Crops Research Department of North Carolina State University, has compared biomass yield of different cultivars commonly used for conventional tobacco agriculture but grown at dense spacing. In 1981, the annual biomass yield ranged from 59 tons/acre for a TI 174 cultivar to 38 tons/acre for a V 174 cultivar. The V 174 cultivar also had a 30 percent less protein yield than TI 174. Selection of the proper cultivar for a particular geographical region evidently will be an important factor in attaining maximum yield of biomass.

To keep ahead of disease problems, new cultivars of tobacco are constantly being developed by plant breeders. In North Carolina, a new cultivar is released from experiment stations to growers about every 5 years. Genes for resistance to diseases found in some cultivars, or even in different species of *Nicotiana*, are transferred by hybridization to cultivars with desirable traits for smoking tobacco. The process of transfering a desirable gene may require several successive hybridizations to eliminate undesirable genes accompanying genes for disease resistance. Some intermediate hybrid cultivars of no use in conventional tobacco agriculture could have characteristics valuable for protein production, such as hybrid vigor and disease resistance.

Inputs Required for Implementation of Technology

Professor Long proposed a system for growing closely spaced tobacco for protein production using conventional nursery practices. A 1-acre nursery would yield enough plants to transplant 9 acres at a density of 84,000 plants per acre while leaving a similar density of plants in the nursery. The biomass from the 10 acres would be harvested four times. Long (6) estimated the following inputs:

1. **Preparation of nursery seed bed. Materials:** Seed, 6.8 oz/acre; fertilizer, 3,400 lb/acre; fungicide and insecticide, 90 lb/acre; herbicide, 13 lb/acre; fumigation, plastic cover, and irrigation ($1,960/acre). **Labor:** fumigation, plowing, fertilizing, sowing seed, etc. (82 hr/acre at minimum wage). **Machinery and Overhead:** tractor, truck, spraying, rolling plastic cover, irrigation (32 hours at average cost of $14.20/hr).
2. **Preparation of land for transplants. Materials:** fertilizer, 1,681 lb/acre ($151/acre); nematicide, herbicide, insecticide ($86/acre). **Labor:** land preparation, spraying, fertilizing (3 hr/acre); transplanting (143 hr/acre at minimum wage). **Machinery and Overhead:** tractor, truck, sprayer, irrigation (36.3 hrs at average cost of $23/hr).
3. **Four harvests of biomass and inputs for three periods of regrowth. Materials:** fertilizer (3,200 lb/acre or $213/acre); herbicide. insecticide ($20/acre). **Labor:** harvesting, hauling, spraying, irrigating (11.7 hr/acre at minimum wage). **Machinery and Overhead:** harvester, tractor, truck, sprayer, irrigation (10.9 hr/acre at average cost of $23/hr).

Adding land rent at $75/acre, irrigation at $120/acre, interest on investment (at 20 percent for 6 months) at $160/acre, and profit at $200/acre, total input cost for the North Carolina transplant system was estimated to be $2,275/acre.

With a direct seeding system of the type used in Florida, input cost was estimated to be $1,900/acre; because of the longer growing season this figure includes five harvests with an annual yield of 75 tons of biomass/acre.

Scientific, Environmental, Economic, Cultural, and Political Aspects of Development and Implementation of Technology

Engineering. As stated earlier, there appear to be no unsolved engineering problems to constrain large-scale expansion of the LPI process. Plants capable of processing 40 tons of biomass per hour have already been used to extract the green juice from alfalfa. For a yield of 60 tons/acre in North Carolina, a 40 ton/hr plant could process the biomass grown on 2,432 acres. The problems remaining before designing such a plant are of a development nature. Additional information is needed to make proper choices among the various types of equipment available to minimize operating costs for labor, power, water, maintenance, and overhead.

Environmental. In the LPI process, no aerial portions of the plants are discarded as waste except the water which comprises 85 to 90 percent of the biomass. The water is removed by evaporation of the brown liquid residue and could be condensed and used again, if economical. To be economically viable, solvent extraction of green residue and green sludge would have to recover the solvent as efficiently as factories engaged in hexane extraction of oil from soybeans. Solvents used in the LPI process are less volatile and have higher flash points than hexane.

Economic. The finished products (table 1) produced from tobacco biomass by the LPI process are tobacco for smoking and food for human consumption. Private industry with manufacturing and marketing expertise in food products may be uncomfortable with the prospect of entering into the manufacture and marketing of a smoking product of equal or higher value than the food product. This constraint could be overcome by organizing a company to construct and operate the factories that make the finished products in table 1, all of which could be stored at ambient temperature. The decolorized white fibers and condensed brown liquid would be supplied to tobacco manufacturers for further processing into smoking material. The proteins would be supplied to food processing manufacturers and pharmaceutical companies. The solvent-extracted pigments could be supplied as raw stock to manufacturers that would refine and market the chlorophyll, beta carotene, carotenoids, solanesol, and other compounds.

Consumer Acceptance. A significant barrier to commercial exploitation of this technology is the public's image of tobacco as a poisonous plant. Tobacco does indeed contain nicotine. However, repeated analyses have been performed on crystalline Fraction 1 protein from tobacco grown to different stages at close spacing and after different rattoon harvests. Nicotine contamination was in the parts per **billion** range, detectable only by the most sophisticated methods of analysis. The contamination was far below the level of 2 parts per **million** (ppm) that the Food and Drug Administration (FDA) considers safe in poultry meat which gets contaminated by nicotine-containing insecticides used in poultry farms. The contamination of Fraction 1 protein is also far below the 2 to 3 ppm nicotine found naturally in tomatoes, eggplant, green peppers, and tea.

Constant reminders of the link between smoking and cancer and other debilitating diseases further exacerbate the negative image of tobacco. Nicotine is not oncogenic. Tobacco has to be burned to produce the oncogenic compounds found in smoke. Smoke from burning leaves or charcoal-broiled steaks also contains oncogenic compounds, but they constitute no significant hazard to health because of the infrequency of inhaling such smoke. So it is not the nicotine nor the possible presence of cancer-inducing chemicals in tobacco proteins that constitute the problem with public acceptance. The problem is tobacco's negative image that is constantly being reinforced by reminders of the harmful effects of smoking. Thus, a food company contemplating the market for products containing tobacco proteins could be faced with an inability to overcome the negative image of tobacco.

If those who see tobacco agriculture and cigarette manufacture as a declining industry in the United States are correct, the best interests of the tobacco industry might be served by educating the public on the virtues of tobacco as food and actively supporting efforts to produce less harmful tobacco for smoking. However, the fact that the tobacco industry steadfastly refuses to accept as proven that smoking is harmful to health makes their promotion of tobacco as food unlikely.

Government could play a decisive role in overcoming the problem of public resistance to the use of tobacco for food. Existing government laboratories could perform the extensive testing of the tobacco proteins required for FDA approval of their use as a food additive. There is scientific evidence indicating that tobacco proteins will receive a clean bill of health after such testing. Then government could exercise a publicity function to ensure widespread dissemination of unbiased data. In this function, the Office of the Surgeon General could be as effective in changing the negative image of tobacco as it has been in educating the Nation on the perils of smoking.

Cultural. As with other crops in the United States, production of the conventional tobacco crop has become increasingly more mechanized as new types of farm equipment have become available. Intensive labor is required only for brief periods during transplanting, harvesting, and curing the crop. The North Carolina transplant system to grow tobacco biomass for the LPI process would require somewhat more labor for transplanting but less for harvesting than the conventional system. Labor requirements would remain about the same so that adoption of the new form of agriculture would have little impact on existing cultural patterns. As direct seeding of tobacco becomes perfected to replace transplantation, tobacco grown for biomass would become as mechanized and capital intensive as corn, soybeans, alfalfa, and other crops.

Political. In the United States, conventional tobacco is grown and marketed under a Government regulated allotment program that limits total acreage in return for a basic support price for cured tobacco. By leasing allotments, some farmers grow 100 or more acres of tobacco using mechanized equipment as much as possible. Because efficient farmers derive high income from tobacco, it is natural that the lessors and lessees of allotments will zealously guard a program so favorable to their welfare. Since the individual allotment is usually less than 3 acres, the number of individuals owning allotments is large, considering that almost 1 million acres of tobacco are grown in the United States. Their votes translate into a significant political force.

Balanced against the political clout of the allotment holders are the public health concerns over the hazards associated with the use of smoking tobacco. These concerns have left their mark; this year Congress required the allotment program to operate without Government subsidies. The program has to be renewed annually by Congress, and each successive renewal vote has become more uncertain.

Impacts on Developed and Developing Countries

Implementation of tobacco as a food crop in European countries would provide an alternate source of protein and decrease the present need to import soybeans that cannot be grown in many parts of Europe. In Japan, which cannot grow enough soybeans to meet its domestic requirement, tobacco would become an additional source of protein to replace some soybean imports. Agriculture in developing countries in the Tropics is notable for lack of crops of high protein content. Soybeans cannot be grown in tropical climates. Tobacco, however, is grown extensively in the Tropics and could become a source of protein not previously available because foreign exchange was not available to import soybeans. Tobacco protein could have tremendous impact by helping to alleviate malnutrition in these countries.

High technology equipment is not required to use tobacco for protein production, and analogs of the equipment used by LPI in the United States are readily available in all industrialized nations. Easy availability of the equipment would help reduce the cost of initiating production of the new food in developing countries. Less developed countries would not have to import scientific know-how because the LPI process is simple. Both domestic and foreign patents of the process have been issued so that the scientific information is available in the patent literature. LPI views a logical development of the technology as starting with a demonstration factory in the United States which could train personnel in the agricultural and processing aspects of tobacco for protein and the other finished products listed in table 1.

When tobacco is grown for protein, the agricultural practice will conform to the existing cultural and social patterns of the country in which it is grown. In the United States, great emphasis will be placed on mechanization. In countries with high population density and land scarcity, cultivation of tobacco for food may remain highly labor intensive. Plants would be transplanted by hand at even closer spacing than can be accomplished by transplanting machines. Fertility, weed control, and harvesting would be managed by people instead of costly herbicides, insecticides, and harvesting machinery, and biomass production per unit of land could exceed that produced by a high degree of mechanization. Labor intensive cultivation of tobacco for protein could also have an impact by reducing the acreage used for smoking tobacco and making the land available to grow other kinds of food crops. For example, China uses about 2.5 million acres for smoking tobacco. If only 30 percent of the LPI deproteinized tobacco were combined with 70 percent conventional tobacco in Chinese cigarettes, about 400,000 acres now used for conventional tobacco could be released because the yield of deproteinized tobacco per acre is about five times greater than conventional tobacco. In addition, enough crystalline Fraction 1 protein would be produced as a byproduct of deproteinized tobacco to satisfy the total annual protein requirement for 2.4 million people, to say nothing of the Fraction 2 protein and insoluble protein produced at the same time. At 100 percent deproteinized tobacco in cigarettes, 2 million acres could be taken out of smoking tobacco and used for much needed food crops.

As in other parts of the world, the Chinese Government has become alarmed by the health hazards caused by smoking tobacco. The health hazards associated with "tar" in burning tobacco have been reduced in Western countries by filters and sophisticated techniques for diluting the smoke with air before it enters the lungs,* but the materials required add appreciably to the cost of cigarettes. Thus, another advantage that could accrue from deproteinized tobacco in developing countries is that a significant reduction in tar producing ingredients would have occurred during processing so that the extra cost of filtration and dilution devices might be avoided.

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*OTA footnote: Readers interested in characteristics of low-yield cigarette use are referred to N. L. Benowitz, et al., "Smokers of Low-Yield Cigarettes Do Not Consume Less Nicotine," *The New England Journal of Medicine*, vol. 309, No. 3, July 21, 1983, pp. 139-142. The article appeared in print while this proceeding was in press.

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Appendix 1

Fraction 1 Protein

Also known as ribulose-1,5-bisphosphate carboxylase-oxygenase, the enzyme that catalyzes the assimilation of carbon dioxide during photosynthesis. Crystals of Fraction 1 protein are insoluble in water even though 80 percent water is an intrinsic part of their structure. Crystals rapidly dissolve in water containing traces of sodium, potassium, or ammonium ions. When dried, the crystalline protein contains no nucleic acid, lipoids, or carbohydrates, and more than 99 percent of its composition is composed of amino acids with the composition shown below:

Amino Acid Composition of Fraction 1 Protein

Amino acid	*g/100 g/protein*	*AA*	*g/100 g*	*AA*	*g/100 g*
Ile	4.3	Thr	5.2	Asp	8.5
Leu	8.8	Try	1.5	Ser	3.3
Lys	5.8	Val	7.2	Glu	11.2
Phe	4.4	His	2.2	Pro	4.6
Tyr	4.9	Cys	3.0	Gly	9.2
Met	1.6	Arg	6.1	Ala	7.0

High nutritional value of Fraction 1 protein shown by feeding rats with the PER results (4) summarized below:

Protein Efficiency Ratio (Weight Gained/Protein Consumed) of Fraction 1 Protein Compared to Casein as Standard

	Days after feeding			
	7	*14*	*21*	*28*
Casein	2.73	3.17	2.88	2.83
Fraction 1 protein	3.40	3.44	3.10	3.01

Exposed to trypsin, one of the digestive enzymes of the human stomach, Fraction 1 protein rapidly breaks down into about 80 tryptic peptides of small molecular weight demonstrating its high degree of digestibility. The native protein contains many sulfhydryl groups but no disulfide linkages.

Functionality studies were performed with three different forms of crystalline Fraction 1 protein: **Crystals,** washed free of salts by water, were spray-dried before testing; **pH 8.5,** washed crystals were redissolved with NaOH to pH 8.5 before spray-drying the redissolved protein; **pH 3.0,** washed crystals were redissolved with NaOH to pH 10.5, then acidified to pH 3.0 with phosphoric acid before drying.

Foaming Capacity and Stability

Sample	*Foaming capacity (ml) after ½ min*	*Foam stability (ml) after 10 min*	*30 min*	*1hr*	*2 hr*
Fraction 1 protein (crystal)	75	48	42	30	24
Fraction 1 protein (pH 8.5)	77	30	14	6	6
Fraction 1 protein (pH 3.0)	82	60	60	58	58
Soy protein*	53	6	6	4	4
Eggwhite	62	18	14	14	10

*A product of Natural Sales Co., Pittsburgh, Pa., All Star, 95 percent protein containing lecithin and papain.

Water and Oil Absorption

Sample	*Water (pH 5 acetate buffer)*	*Crisco oil*
	Percent weight increase	
Fraction 1 protein (crystal)	180.7	105.8
Fraction 1 protein (pH 8.5)	319.0	304.5
Fraction 1 protein (pH 3.0)	393.3	375.5
Soy protein	272.1	187.5
Eggwhite	466.9	144.4

Whipping property

Sample	*Volume increase after whipping*	
	Before add'n of sugar	*After add'n of sugar*
Fraction 1 protein (crystal)	673%	780%
Fraction 1 protein (pH 8.5)	570	640
Fraction 1 protein (pH 3.0)	633	670
Soy protein	none	none
Eggwhite	600	633

Emulsifying Property

	Protein concentration			
Sample	*1%*	*2%*	*4%*	*6%*
1. 40% oil				
Fraction 1 protein (crystal)	18 cps	26 cps	45 cps	97 cps
Fraction 1 protein (pH 8.5)	30	33	117	284
Fraction 1 protein (pH 3.0)	44	535	10379	too thick
Soy protein	40	140	978	18915
2. 40% oil + 1% each of NaCl and starch				
Fraction 1 protein (crystal)	21	41	166	690
Fraction 1 protein (pH 8.5)	55	126	343	681
Fraction 1 protein (pH 3.0)	26	30	112	146
Soy protein	30	52	151	481
3. 20% oil				
Fraction 1 protein (crystal)	8	8	12	25
Fraction 1 protein (pH 8.5)	6	22	45	99
Fraction 1 protein (pH 3.0)	43	281	539	5941
Soy protein	35	127	442	696
4. 20% oil + 1% each of NaCl and starch				
Fraction 1 protein (crystal)	8	28	28	55
Fraction 1 protein (pH 8.5)	28	55	133	159
Fraction 1 protein (pH 3.0)	4	9	11	139
Soy protein	5	10	29	55

Appendix 2

Fraction 2 Proteins

Amino Acid Composition

Amino acid	*g/100 g protein*	*AA*	*g/100 g*	*AA*	*g/100 g*
ASP	6.1	ALA	5.1	PHE	8.4
THR	4.6	VAL	10.5	LYS	3.9
SER	4.0	MET	4.1	HIS	5.0
PRO	8.2	ILE	3.8	ARG	10.4
GLU	8.9	LEU	4.1	CYS	0.8
GLY	3.5	TYR	8.8		

Appendix 3

Green Sludge

Essential Amino Acid Composition of Green Sludge Protein Compared With Soyflour Protein

	g/100 g Protein	
Amino acid	*Soyflour protein*	*Tobacco insoluble protein*
THR	3.6	4.4
MET	1.0	1.8
ILE	3.5	4.1
LEU	6.4	4.2
TYR	2.1	9.6
PHE	4.7	8.8
LYS	5.1	3.9

Appendix 4

Green Residue

Chemical Composition of Dried Green Residue From Tobacco (Average of Four Different Preparations)

	mg/g		*mg/g*		*% of ash*		
Protein	148	Ash	53	K	0.6	Ma	0.2
Starch	30	Cellulose	291	Ca	0.6	S	0.2
Lipids	20	Hemicellulose	413	Mg	0.15		
Lignin	45						

Comparison in Composition Between Green Residue Decolorized by Solvent Extraction and Wheat Bran

	Percent total solids	
Constituent	*White tobacco fibers*	*Wheat bran*
Cellulose	29	9
Hemicellulose	33	40
Lignin	6	4
Starch	13	17
Protein	13	18
Oil	trace	4
Ash	7	8

Appendix 5

Low Molecular Weight Compounds

Protein, Nicotine, and Apparent Tar Content of LPI Deproteinized Cigarette Tobacco Compared With Two Kinds of Conventional Cigarette Tobacco

	Percent dry weight		
Product	*Protein N*	*Nicotine*	*Tar*
Conventional flue-cured tobacco, variety NC 95	2.25	2.0	6.77
Deproteinized NC 95	1.84	0.6	0.70
Conventional burley tobacco, variety KY 14	4.15	3.0	6.07
Deproteinized KY 14	3.00	0.7	0.82

Leaf Protein Extraction From Tropical Plants

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ABSTRACT

Protein and calorie malnutrition is widespread in the less developed countries. Importing high-grade animal products, cereal grains, and animal feeds puts a strain on these countries' economies. Leaf protein concentrates (LPCs) should be seriously considered as additional protein sources. Leaf protein concentrates from alfalfa are prepared on a large commercial scale in Europe and the United States. Unfortunately, alfalfa has not been grown successfully in the humid tropics, and a suitable tropical replacement is needed for leaf protein extraction.

At least 500 introductions of tropical plants have been tested at the U.S. Department of Agriculture's (USDA's) Tropical Agriculture Research Station in Puerto Rico. Potential plants for LPC production have been evaluated and selected for further research. Machinery has been developed which may be suitable for laboratory, on-farm, village level, and commercial extraction. Further research is needed in agronomy and leaf protein extraction and use. On-farm use is the most economical system for the tropics. It is suggested that crude leaf protein concentrate be used as human food only in extreme emergencies.

Tropical Plants for Leaf Protein Extraction

At the present growth rate, world population will double in the next 30 to 40 years. This population increase mainly will burden the lesser developed countries in the humid lowland tropics, where the current annual population growth rate is 2.3 percent and yearly increase in food production remains low. The demand for food of plant origin will continue to increase, and the supply of meat will decrease because yields of cereal grains in the tropics generally are low and local production is consumed by humans. This ever-widening food shortage cannot be alleviated by conventional agriculture alone. As an additional source of protein, leaf protein concentrates (LPCs) should be given serious attention because leaves are abundant year-round in the tropics and many have high protein content. With suitable plant material, the yield per hectare per year of leaf proteins can be at least four times higher than that of seed proteins.

Leaf protein concentrates for animal feed currently are manufactured from alfalfa in Europe, and a new processing plant was started recently in the United States. Because efforts to adapt alfalfa to the tropics have been only marginally successful in a few areas, possible tropical plant sources have been investigated.

In 1978, a broad research program to find suitable tropical plants for leaf protein fractionation was organized at the Tropical Agriculture Research Station, USDA (Science and Education) in Mayaguez, Puerto Rico. At least 500 introductions were planted and critically evaluated as potential sources for LPC extraction (77) (table 1). The following criteria were used in selecting plants suitable for LPC production: high protein and dry matter (DM) content, good protein extractability when freshly cut, and good regrowth potential. The plants should fix nitrogen, be erect and easily harvested mechanically, and be nontoxic and low in antinutritional factors.

Freshly harvested plants were extracted in a blender with 600 ml ice water at high speed for 5 to 10 minutes and filtered in a bag made of closely woven fabric. The pressed green juice was heated carefully in a 2-liter Erlenmeyer flask immersed in boiling water and agitated with a slow motion stirrer. At 55° C, a green coagulum formed and was separated by centrifugation, washed several times, and finally spread in thin layers on glass plates and dried. The supernatant from the centrifugation was heated carefully to 64° and the white curd coagulum that formed was separated by centrifugation, washed with acetone, and dried in a rotary evaporator. The liquid was further heated to 82°. After cooling, a light tan precipitate formed and was processed as the 64° fraction (see fig. 1).

The spontaneous coagulation of protein in the juice extracted from some plants was observed during the survey of tropical plants. This phenomenon occurred during extraction of leaves of cassava, *Leucaena leucocephala;* some *Indigoferas, Desmodium, and Mimosa* species; and many of the tree legumes of Mimosa, Cassia, and Pea subfamilies. These plants have been classified as Type I (table 1). Another group of plants yielded a green

Table 1.—Crude Protein Content of Tropical Plants

Plant	Origin	Percent		Type[a]
		Dry matter	Crude protein	
AMARANTHACEAE				
Amaranthus anclancalius	Hungary	12.3	26.6	IV
A. caudatus	Sweden	13.0	27.7	IV
A. cruentus	Taiwan	14.6	28.3	IV
A. gangeticus	Hungary	14.5	24.4	IV
A. hypochondriacus	Sweden	11.5	27.9	IV
A. mantegazzianus	Sweden	16.2	30.0	IV
COMPOSITAE				II
Helianthus uniflorus	Hungary	26.6	29.9	II
H. annuus	Sweden	24.6	25.4	
CRUCIFERAE				
Brassica alba	Hungary	22.5	39.8	III
B. campestris	Pakistan	14.2	19.1	III
	Guatemala	10.8	21.0	III
B. hirta	Yugoslavia	10.4	30.0	III
	Poland	12.6	30.8	III
B. napus	Hungary	11.8	21.1	III
	France	11.6	26.4	III
	China	14.4	24.4	III
Brassica juncea	India	13.8	27.1	III
	Cuba	12.2	22.3	III
	Nepal	14.2	24.8	III
B. nigra	India	10.2	26.4	III
	Turkey	10.8	24.0	III
	Greece	14.1	20.6	III
B. oleracea	United States	14.0	19.4	III
B. " var. gongyloides	United States	12.6	19.4	III
Lepidium sativum	Puerto Rico	12.3	17.6	III
Nasturtium officinale	Puerto Rico	18.2	22.6	IV
CUCURBITACEAE				
Benincasa hispida	India	18.0	18.0	II
Lagenaria siceraria	S. Africa	11.4	26.3	II
Luffa cylindrica	India	19.3	26.3	II
EUPHORBIACEAE				
Cnidoscolus chayamansa	Mexico	18.8	26.3	II
Manihot esculenta	Colombia	20.8	25.5	I
LEGUMINOSAE				
Aeschynomene falcata	Brazil	20.2	13.5	III
A. scabra	Mexico	20.8	15.5	III
A. indica	India	20.8	16.9	III

Alysicarpus vaginalis	India	20.1	20.0	III
	Ceylon	18.6	20.3	III
Cajanus cajan	India	24.0	22.5	III
	Mexico	2 .0	20.6	III
Calopogonium muconoides	Indonesia	20.0	19.7	III
Canavalia ensiformis	India	21.5	18.4	III
	Brazil	19.8	22.1	III
C. gladiata	Philippines	20.9	21.9	III
Centrosema pubescens	India	23.5	18.9	III
	Philippines	25.0	23.2	III
	Ivory Coast	20.0	19.4	III
Clitoria ternatea	Brazil	16.1	23.6	III
	Cuba	20.6	23.0	III
	Australia	19.2	24.3	III
Crotalaria alata	India	18.6	19.9	II
C. argyrolobioloides	Kenya	20.4	23.9	II
C. brachystachya	Brazil	19.2	27.4	II
C. incana	Argentina	19.3	22.9	II
C. juncea	India	21.4	25.8	II
	USSR	24.0	26.3	II
Cyamopsis tetragonoloba	India	14.2	19.2	III
Desmodium canum	Brazil	20.8	18.9	I.
D. distortum	Hawaii	16.8	17.8	III
D. intortum	Spain	25.0	18.7	III
	Brazil	25.0	23.5	III
D. perplexum	Brazil	20.0	16.2	II
D. sandwicense	Australia	21.7	23.0	I
Glycine wightii	S. Africa	19.2	19.6	III
Indigofera arrecta	Ghana	31.2	15.1	II
I. brevipes	Costa Rica	18.3	26.8	II
I. cireinella	Korea	17.6	26.2	I
	S. Africa	16.4	28.1	I
I. colutea	Australia	20.2	28.7	III
I. confusa	Indonesia	19.8	14.6	II
I. cryptantha	S. Africa	19.6	24.0	III
I. echinata	Tanzania	21.0	21.4	II
I. hirsuta	Nigeria	22.1	24.2	II
	Brazil	21.0	27.9	II
	Rhodesia	23.4	30.6	II
I. hochstetteri	Rhodesia	18.3	21.2	II
I. microcarpa	Argentina	34.9	22.3	II
I. mucronata	Peru	20.8	22.4	II
	Brazil	23.7	24.4	II
I. retroflexa	Kenya	21.8	21.2	II
I. schimperi	Africa	14.6	23.3	II
I. semitijuga	India	31.8	17.2	II
I. spicata	Tanzania	16.5	35.7	II
I. subulata	Kenya	27.2	12.3	II
	Cuba	26.4	10.8	II
I. suffruticosa	Brazil	21.4	25.3	II
	Mexico	20.7	32.4	II
I. sumatrana	Australia	21.8	28.2	II
I. tetlensis	Africa	20.2	20.5	III
I. teysmannii	Malaya	21.6	31.0	II
I. tinctoria	Dom. Republic	20.6	15.2	II

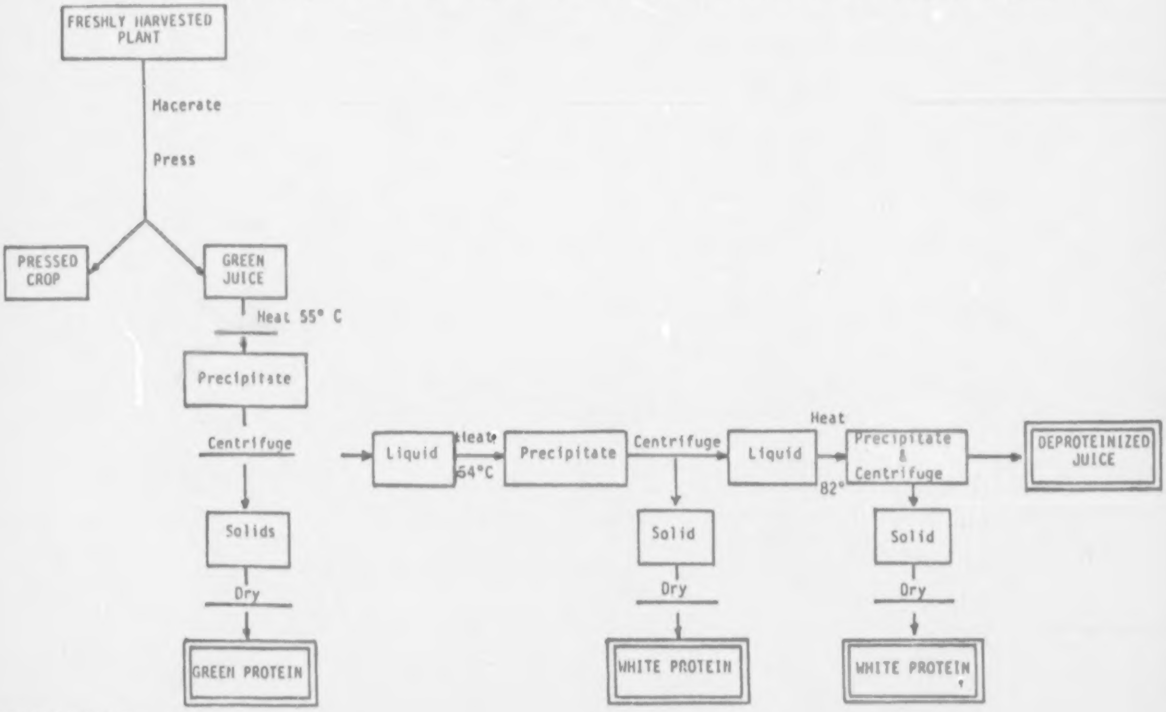
Lablab purpureus	Malaysia	21.5	27.7	III
Lupinus albus	Turkey	18.8	19.5	III
L. angustifolius	Hungary	20.4	18.8	III
	S. Africa	22.6	16.6	III
L. luteus	Hungary	22.2	16.1	III
	Spain	20.4	19.2	III
L. hispanicus	Portugal	20.6	19.8	III
	Spain	20.2	19.2	III
Macroptilium lathyroides	Australia	18.8	19.5	III
Macrotyloma uniflorum	Puerto Rico	18.6	26.4	III
	South Africa	21.0	21.3	III
Mucuna deeringiana	Mozambique	17.2	32.6	II
Phaseolus acontifolius	India	18.8	18.3	III
	Afghanistan	22.2	15.8	III
P. calcaratus	Ivory Coast	19.7	20.8	III
	Honduras	20.1	23.7	III
Psophocarpus tetragonolobus	Puerto Rico	20.6	22.0	III
Sesbania arabica	Turkey	21.8	29.9	III
	Afghanistan	22.2	30.0	III
S. cannabina	India	19.8	21.4	III
S. exasperata	Brazil	20.4	20.9	III
	Argentina	20.6	20.6	III
S. macrocarpa	Australia	22.0	19.2	III
	Mexico	19.8	19.9	III
S. sesban	India	20.6	27.6	III
	China	19.4	29.4	III
Stizolobium aterrimum	Mexico	20.6	27.4	III
Stylosanthes gracilis	Paraguay	21.2	22.3	IV
S. humilis	Australia	22.0	20.9	IV
	Brazil	21.8	18.9	IV
Tephrosia adunea	Venezuela	22.2	18.0	II
T. cinerea	Uruguay	24.2	14.0	II
T. incana	Kenya	23.8	19.3	II
	Indonesia	24.4	21.4	II
T. noctiflora	Brazil	23.6	13.2	II
T. vogelii	Puerto Rico	20.4	12.3	II
Vigna mungo	Pakistan	19.3	23.6	III
	China	21.0	24.0	III
	Iran	19.3	16.9	III
V. radiata	Turkey	18.9	22.9	III
	India	21.1	22.2	III
V. unguiculata	Guatemala	18.8	19.5	III
	Mexico	19.0	19.4	III
Zornia brasiliensis	Brazil	20.2	15.8	III
Z. diphylla	Brazil	19.8	16.8	III
Z. latifolia	Brazil	20.0	15.8	III
MALVACEAE				
Abelmoschus manihot	Japan	14.6	14.0	III
SOLANACEAE				
Capsicum annuum	Yugoslavia	20.0	22.4	III

Capsicum annuum	Ecuador	12.5	19.9	III
	Israel	20.0	21.8	III
C. chinense	Georgia-USA	15.3	20.0	III
	Guatemala	15.3	23.4	III
	Colombia	16.7	19.9	III
C. pendulum	Mexico	18.0	19.8	III
	Chile	22.2	21.0	III
	California-USA	16.0	20.2	III
Solanum melongena	India'	21.0	21.2	III
	China	21.4	21.4	III

[a] Yield of different fractions after extraction: I. Only one green fraction coagulated at room temperature; II. One green fraction on heating to 55°C and one minute amount of light tan fraction at 82°; III. One green fraction at 55°, one white fraction at 64° and another light tan fraction at 82°; IV. No distinct separable coagulum by heat fractionation.

SOURCE: Telek (77).

Figure 1.—Laboratory Method for Preparation of Protein Concentrate From Tropical Plants


FRESHLY HARVESTED PLANT
Macerate
Press
PRESSED CROP
GREEN JUICE
Heat 55° C
Precipitate
Centrifuge
Solids
Dry
GREEN PROTEIN
Liquid
Heat
64°C
Precipitate
Centrifuge
Solid
Dry
WHITE PROTEIN
Liquid
Heat
82°
Precipitate & Centrifuge
Solid
Dry
WHITE PROTEIN
DEPROTEINIZED JUICE

SOURCE: Telek (77).

protein coagulum after the extracted green plant juice was heated to 55° C and yielded a very small quantity of a light tan precipitate at 82° C. This first was observed with leaf protein extract of sorghum-sudan grass hybrids and other grasses. Plants of this group have been classified as Type II. Type III is the most important group of plants. Careful heat fractionation of aqueous leaf extracts yielded three distinct protein fractions: a green coagulum at 55° C, a copious white protein precipitate at 64° C, and a smaller amount of a light tan precipitate at 82° C. The most desirable plants for further studies were selected from this group (table 2). A final group, designated as Type IV, includes plants in

Table 2.—Selected Plants for Leaf Protein Concentrates Production

Plants	Dry matter yield Mg/ha/year	% Protein of dry matter	% protein extractability	Biological nitrogen fixation	Regrowth
Brassica napus	28	25.4	62.4	-	Poor
Centrosema pubescens	12	18.8	37.2	+	Good
Clitoria ternatea	28	24.0	59.8	+	Good
Desmodium distortum	11	18.0	47.9	+	Good
Lablab purpureus	19	28.4	58.1	+	Good
Macroptilium lathyroides	12	26.0	59.0	+	Good
Psophocarpus tetragonolobus	20	22.2	53.6	+	Fair
Sesbania sesban	20	28.6	40.2	+	Fair
Vigna radiata	16	22.9	47.8	+	Fair
V. unguiculata	25	19.5	52.0	+	Fair

SOURCE: Telek (77).

which the proteins in the aqueous extracts do not precipitate either spontaneously or after heat treatment. This was observed in extractions of *Stylosanthes gracilis, S. humilis, Nasturtium officinale*, and *Amaranthus* spp.

Pilot Plant Scale Preparation and Nutritional Evaluation

Leaf protein concentrates from the tropical legumes *Leucaena leucocephala, Vigna unguiculata, Clitoria ternatea, Desmodium distortum, Psophocarpus tetragonolobus, Macroptilium lathyroides, Phaseolus calcaratus, Brassica napus*, and *Manihot* esculenta were prepared on a pilot plant scale. The plants were harvested in the vegetative stage of growth, stored in a freezer, transported in a frozen state, and processed in the pilot plant of the Food Technology Laboratory, University of Puerto Rico. Processing consisted of chopping to 2-cm pieces followed by soaking in 2-percent sodium metabisulfite. The soaked material was disintegrated in a hammer mill and pressed in a single-screw press. The expressed juice was heated with steam to 82° C until a protein coagulum appeared. The hot coagulum was collected in a basket centrifuge, pressed in a canvas bag under a hydraulic press, spread in a thin layer on glass plates, and dried in an air-conditioned, dehumidified room. The pressed green juice of *Leucaena leucocephala* and cassava was left for 20 hours for self-precipitation of proteins at ambient temperatures (29° to 31° C). The settled precipitates were processed as outlined above.

The protein quality of the LPC was evaluated by using rats (17). The tropical legumes *Vigna unguiculata, Desmodium distortum, Phaseolus calcaratus*, and *Psophocarpus tetragonolobus* gave excellent results, comparable to those obtainable from alfalfa LPC. These plants have low polyphenol contents. Another legume low in phenols, *Macroptilium* lathyroides, gave relatively poor results (table 3) due to its high saponin content. The differences in rat growth probably are due to different amino acid availabilities, as influenced by polyphenols and other compounds that may react with protein to form indigestible complexes.

The LPCs from the tropical legumes tested were found to have amino acid contents similar to each other and to reported values for alfalfa LPC and soybean meal (table 4).

Cassava and *Leucaena* were included in this nutritional evaluation, alongside the selected plant sources, to support our classification of plants based on the number of protein fractions. It was suspected that the spontaneously precipitated protein concentrate from Type I plants would have less nutritional value. Rats fed LPC from cassava and *Leucaena* grew poorly. The data showed that protein concentrates from these plants cannot be produced by the accepted LPC processes.

About two decades ago, the use of tree leaves as a potential source of leaf protein concentrate was suggested (60,64), and their possible use is still being mentioned in literature. The presence of phenolic substances negatively affects the nutritional value of the proteins prepared from tree leaves. After our studies of *Leucaena leucocephala*, we extended our investigations to the other tree legumes located in Puerto Rico. The Leguminosae family is huge (14,000 species) and extremely diverse, ranging from forest trees to shrubs to herbaceous annuals.

The results of our investigations, given in table 5, clearly indicated that, with current methods,

Table 3.—Protein Content of Tropical Plant LPC, Diet Composition, and Rat Growth Performance

	Diet Composition				Rat Performance			
Source of LPC	Crude Protein (%) of LPC[1]	% LPC	% Corn	% Soybean Meal	Avg. Daily Gain[2] (g)	Avg. Daily Gain as % of Control	Avg. Daily Feed Intake[2] (g)	Protein Efficiency Ratio
Corn-soy control	----	----	69	22	7.2±.4^{f}	100	16.4±1.5	2.7
Leucaena leucocephala	31.3	31.9	57	2.1	0.9±.4^{h}	12.5	11.0±1.8	0.4
L. Leucocephala (acetone-washed)	38.2	26.1	64.5	0.4	0.7±.1^{h}	9.7	11.6±1.9	0.4
L. leucocephala (acid-washed)	28.2	35.5	52.7	2.8	1.0±.9^{h}	13.9	9.7±1.4	0.5
Manihot esculenta[3]	36.2	27.6	62.6	0.8	1.8±.2^{gh}	25.0	11.7± .9	0.9
M. esculenta[4]	32.1	31.2	58.1	1.7	2.0±.5^{gh}	27.8	11.1±1.2	0.8
M. esculenta[3]	33.3	30.0	59.6	1.4	1.2±.3^{gh}	16.7	11.7±1.9	0.6
M. esculenta (acetone-washed)	41.4	24.2	66.8	---	2.0±.4^{gh}	27.8	14.8±1.7	0.8
Vigna unguiculata	51.9	19.3	71.7	---	5.8±.9^{f}	80.6	18.2±1.8	2.0
Clitoria ternata	59.3	16.9	74.1	---	6.7±.4^{f}	93.1	17.7±1.6	2.4
Desmodium distortum	36.5	27.4	62.8	0.8	5.4±1.0^{f}	75.0	13.0±1.1	2.0
D. distortum (acetone-washed)	47.0	21.3	69.7	---	6.6±.9^{f}	91.7	16.6±2.0	2.3
Psophocarpus tetragonolobus	51.9	19.3	71.7	---	6.0±1.0^{f}	83.3	17.2±1.3	2.2
Macroptilium lathyroides	44.6	22.4	68.6	---	3.0±.5^{g}	41.7	14.9±2.0	1.3
Phaseolus calcaratus	38.0	26.3	64.2	0.5	6.0±.6^{f}	83.3	13.5±1.2	2.1
Brassica napus cv. Early Giant	40.4	24.8	66.1	0.1	6.1±.9^{f}	84.7	17.4±1.5	2.1

[1] N X 6.25

[2] Mean ± standard deviation. Means followed by different letters differ at p 0.01.

[3] Dried in microwave oven.

[4] Dried in air-conditioned room.

SOURCE: Cheeke (17).

good quality leaf protein concentrates for nonruminants could not be prepared from many of the leguminous tree leaves, especially those of Type I plants. However, some of the leaves of the Leguminosae definitely could be used as feed for ruminants after careful analysis for toxic ingredients.

Stylosanthes humilis and *S. guianensis* offered promise for leaf protein extraction. These valuable pasture plants are perennial legumes with high DM yield and a protein content that is as high as that of alfalfa. However, during maceration of these plants, a thick emulsion formed which could not be separated from the fibrous material either by centrifuging or by pressing. On heating, the emulsion thickened and separation became even more difficult. After unsuccessful processing experiments with 10 different cultivars, further research was abandoned.

The lush vegetation of the humid tropics is often considered to have a high potential for animal production. The grasses are an extremely large family of more than 10,000 species. Tropical grasses have a capacity for photosynthetic high rates, grow year round, and show excellent regrowth after repetitive cutting. However, the natural nitrogen (N) content of grasses is relatively low and heavy nitrogen fertilization is required for high DM production.

Our experiments with forage sorghum (Millo Blanco) and sudan hybrids showed encouraging yields (71). However, the extractions were disappointingly low: 28.6 percent extractable protein compared with 52.4 percent for legumes. Investigations of tropical grasses as sources for leaf protein extraction were suspended. It was concluded that the ever-increasing cost of nitrogen fertilizer, the higher processing costs due to lower crude protein content, low extractability of tough fibrous plant material, higher energy requirement of the disintegrator, and the lower quality of protein would make the process uneconomical. With a low initial N content, the extraction of protein from grasses could reach the point where the pressed residue, the most important byproduct, could not be used by ruminants.

Our relatively short systematic investigation of possible tropical plant sources for leaf protein extraction and fractionation produced the following valuable results:

1. Plants equivalent to alfalfa in yield, extractability, and nutritional quality were selected.
2. It was recognized that in the Tropics a single crop cannot be used for year-round production; a pattern of different plantings has to be formulated for rainy and dry seasons. Hollo

Table 4.—Essential Amino Acid Composition of LPC From Tropical Species

Source of LPC	gm amino acid/100 g recovered amino acids									
	Arg	Hist	Isol	Leu	Lys	Meth	Phe	Thr	Val	1/2 cyst
Leucaena leucocephala	6.4	2.2	5.0	9.1	6.3	2.4	5.9	4.8	6.0	0.7
Manihot esculenta[a]	6.3	2.4	5.4	4.3	6.5	2.5	7.0	4.9	6.0	0.8
Manihot esculenta[b]	6.0	2.4	5.2	9.1	6.4	2.4	6.8	5.2	5.7	0.7
Vigna unguiculata	6.7	2.4	5.4	9.4	5.8	2.7	7.5	5.3	6.4	0.6
Clitoria ternatea	6.1	2.2	5.8	9.1	6.1	2.4	7.2	5.2	6.2	2.0
Desmodium distortum	6.1	2.6	5.5	9.4	6.5	2.6	7.3	5.0	6.0	0.6
Psophocarpus tetragonologus	6.2	2.6	5.4	9.3	6.4	2.5	7.1	5.2	6.4	0.6
Macroptilium lathyroides	6.6	2.5	5.6	9.7	5.4	2.7	7.5	5.0	6.4	0.6
Phaseolus calcaratus	6.0	2.5	5.4	9.2	6.4	3.0	7.1	5.1	6.2	0.7
Brassica napus	6.2	2.6	5.3	9.3	5.8	2.6	7.5	5.3	6.4	0.7
Medicago sativa[c]	6.5	2.3	5.6	9.3	5.9	2.3	5.9	5.1	6.3	0.6

[a] Dried in air conditioned room.

[b] Dried in microwave oven.

[c] Kuzmicky and Kohler (1977).

SOURCE: Cheeke (17).

and Koch's (32) statement that "When it is possible to use the raw material of one or only a few plant cultures—e.g., in tropical regions, the technological problems are not as great" now seems inaccurate.

3. Our studies seriously question the popular belief that cassava, *Leucaena leucocephala*, other tropical tree leaves, and tropical grasses are potential sources of LPC.
4. The protein pattern, or number of protein fractions obtained by heat fractionation, was discovered to be a rapid preliminary method to screen plants for protein extraction potential. Type I plants have a low probability of yielding good LPC.

Machinery of Leaf Protein Fractionation

The development of economical equipment for successful farm-size leaf protein processing is a major task. Hjalmar Bruhn (14), a leading authority in the United States on farm machinery designed especially for protein extraction wrote: "I don't see much hope for any appreciable protein production unless there are well engineered machines that are commercially available at farm machinery prices."

The separation of plant juice from the fiber is a two-step process: The rupture of the plant cells by maceration and the separation of the juice and fiber. Cell rupture is the most energy intensive process in leaf protein extraction.

Macerating

Initially, macerating sugarcane rollers were used, but such equipment proved to be ineffective. The overall capacity was low when operating under higher pressure, the power requirement was high, and the machine was very heavy for portable farm use.

Varying degrees of cell disintegration can be accomplished by hammer mills of different construction. These should be used when a high percentage of protein is to be extracted, when the initial plant material has a high protein content, or when the pressed crop will not be used as forage for cattle.

The evolution of small equipment designed in Rothamsted Experimental Station in England

Table 5.—Protein Content of Leaves of Tropical Legume Trees

	% Protein	Plant type
1. *Cassia* Subfamily (Caesalpinioideae)		
Bauhinia alba	17.43	I
Bauhinia candida............	13.20	
Bauhinia galpini............	16.22	I
Bauhinia purpurea...........	8.92	I
Bauhinia reticulata.........	12.59	I
Bauhinia violacea...........	11.80	III
Brownea grandiceps..........	6.47	I
Brownea macrophylla.........	8.58	I
Cassia moschata.............	14.24	III
Cassia nodosa...............	22.85	I
Cassia spectabilis..........	25.90	III
Delonix regia...............	10.57	I
Libidibia punctata..........	14.89	I
Tamarindus indica...........	10.03	I
2. *Mimosa* Subfamily (Mimosoideae)		
Albizia adinocephala........	20.80	III
Calliandra inaequilatera....	14.77	I
Calliandra surnamensis......	16.60	I
Enterolobium cyclocarpum....	26.58	I
Inga laurina................	18.34	I
Inga vera...................	21.44	I
Leucaena leucocephala.......	26.80	I
Parkia biglandulosa.........	12.85	I
Pithecellobium dulce........	18.43	III
Samanea saman...............	17.41	III
3. Pea Subfamily (Faboideae)		
Dalbergia sissoo..........	12.91	III
Erythrina poeppigiana.....	19.13	III
Erythrina variegata orientalis..............	17.94	III
Myrospermum frutescens....	19.42	III

SOURCE: Telek, unpublished.

before 1960 has been published by Davys and Pirie (19). Later, to standardize processing methods, new equiment was built and evaluated in several countries. The new pulper contains 58 fixed beaters with 2 mm clearance from the drum. The rotor is driven by a 5-horsepower (HP) motor. Field experimentation has shown that units can be mounted on a Landrover whose engine drives the pulper. The standard model takes 1 kg crop/min, but could be increased to 6 kg/min. The capacity to macerate 360 kg/hr makes this pulper useful at the village production level (61).

The large-scale fractionation machinery at the National Institute of Research on Dairying (NIRD), Shinefield, England, was developed from a design of Davys and Pirie (20). The pulper has 32 arms that rotate in a cylinder and are driven at 1,100 rpm by a 32.3 HP motor. The total power requirement is 6 to 8 kilowatt hours per metric ton (kWh/MT) of initial crop. More powerful disintegrators of this type were built for the large industrial process. These machines will not be discussed in detail, since they are not related yet to tropical production.

The most energy efficient way to macerate at high capacities is by using extrusion, where the plant material is forced through an orifice (50). High capacity rotary extrusion macerators have been designed by Basken (5) and Nelson, et al. (56). These macerators consist of an internal roller operating against a die ring perforated by radial orifice holes. One of these experimental macerators operated with 22.1 MT/hr capacity at a power input of about 1.7 kWh/MT (fig. 2).

Pressing

The performances of the double screw, single screw, and belt presses used in leaf protein preparation in British research and a commercial crop drying plant were evaluated by Shepperson, et al. (68). Screw presses are effective machines for removing juice from the macerated forage, but their energy consumption is higher than that of some other press designs due to rubbing and shearing action in the press. Industrial screw presses are expensive and less suitable for mobile installation (fig. 3). Platen presses have been used in small or medium installations and can have a capacity of 1.8 to 3.6 MT/hr. The power consumption is low. Belt presses were found to have limitations in the forage dewatering process because maximum pressure is limited by the nature of belt tensions. If new synthetic belts could be produced, this system could be built as relatively light equipment. Several presses for LPC production were described by Pirie (61) (fig. 4). A commercially available cone press was evaluated by Koegel, et. as. (51) and gave satisfactory results for final moisture content and energy requirement. A new press was designed with a cpacity to press 16.5 MT/hr of freshly macerated material to a final moisture content of 65 per cent or less. The weight of the press is 3.1 kg. The results of the evaluation of the cone press for forage fractionation were reported by Straub and Koegel (73), who suggested some changes in cone rotation speed. The average total energy required for the press was low; 0.95 KWh/MT. The sum of energy requirements for macerating alfalfa and pressing it in the cone press is about 3.25 kWh/MT (Nelson et al, 1981). Energy

Figure 2.—Rotary Extrusion Macerator

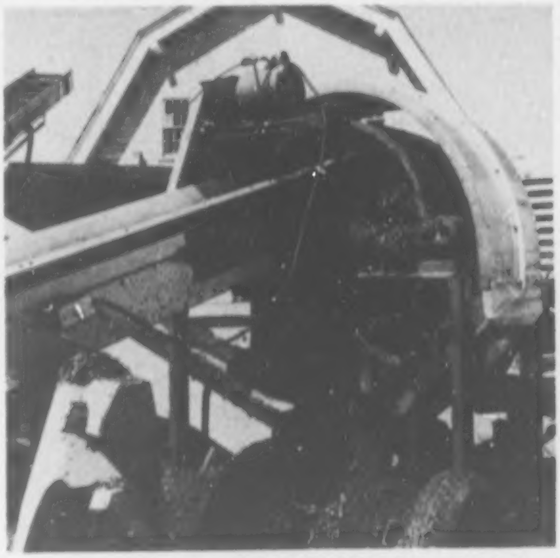


Photo credit: Courtesy of H. D. Bruhn and R. J. Koegel

Figure 3.—MINIPRESS MI IB.

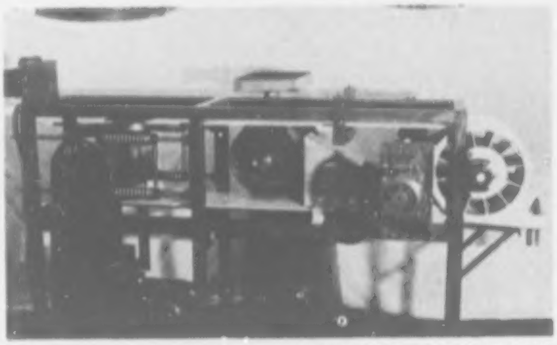


Photo credit: Courtesy of N. W. Price

Figure 4.—Cone Press

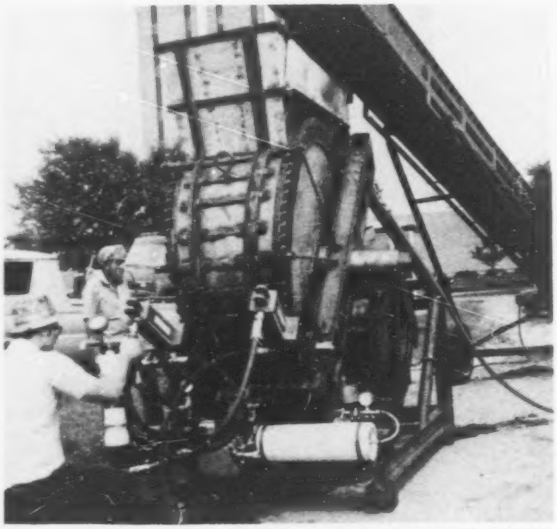


Photo credit: Courtesy of H. D. Bruhn and R. J. Koegel

requirements for maceration and pressing of freshly harvested forage are compared in table 6.

Professor Bruhn (14) converted meat grinders into good, medium, and miniature size systems for laboratory evaluations to replace Waring blenders (fig. 5). The high-speed electric blenders do not duplicate industrial crushers; they chop the fibers into small particles, which will be mixed into the green leaf protein concentrate during the heat-coagulation process.

Separation of Protein Concentrate

Juice, if not directly fed to animals, should be processed without extensive delay. Separation of protein is accomplished by several methods (table 7); however, the most convenient is coagulation by steam injection. An automatic system was developed by Straub, et al. (75), to coagulate the juice and separate the coagulated protein from the brown juice. The incoming juice was preheated by a heat

Table 6.—Energy Requirements for Producing Leaf Protein Green Juice

Process	kJ/kg	hp/h/ton	Reference
Field harvesting			
Direct cut and chop	3 - 7.5	1 - 2.5	ASAE Yearbook, 1975
Maceration			
Extrusion	7.5 - 30	2.5 - 10	Basken *et al.*, 1975
Roll crushing	15 - 90	5 - 30	"
Hammer milling	42 - 150	15 - 50	"
Hammer milling	16.5	5.5	Carroad *et al.*, 1980
Pressing			
Screw press	6 - 30	2 - 10	Basken *et al.*, 1975
Roll press	15 - 30	5 - 10	"
High-cycle platen	15 - 30	0.5 - 1	"
Cone	---	1.14	Bruhn and Koegel, 1982

SOURCE: Compiled by Telek, 1983

Figure 5.—Rebuilt Meat Grinder as Miniature Screw Press

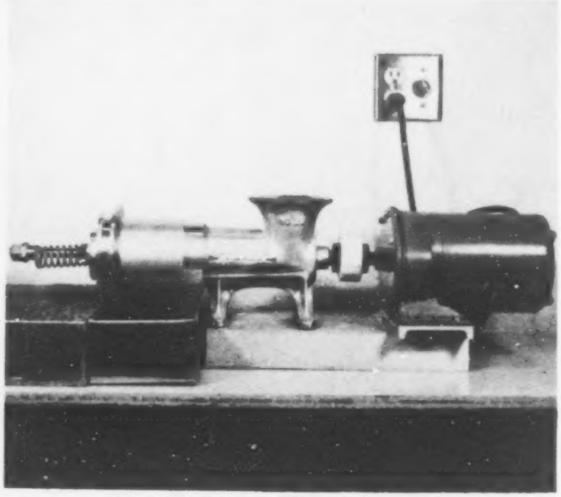


Photo credit: Courtesy of H. D. Bruhn

exchanger, salvaging the heat from the brown juice. The generally accepted energy requirement is 50 kg of steam/MT green crop.

Low-cost and simple technology systems for leaf protein separation and recovery using on-farm level operations have been reviewed by Straub, et al. (74). A farm-scale centrifuge designed to separate suspended solids from animal waste was evaluated. It had a slower than expected acceleration rate and the through-put rate was low: 5 kg/min. Other systems were designed based on flotation, consisting of a stainless steel tank (0.25 m x 0.36 m x 2.64 m) with a working capacity of 211 liters and a built-in steam injector. The flow rate was 42 l/min with a hold time of approximately 5 minutes for flocculation in the tank. The mechanical skimmer was rotated at a speed of 2.3 m/min, and the paddles were immersed in the tank to 5 cm below the spillway (fig. 6).

The belt filtration system consisted of an 8.5-m long continuous woven polyester belt with a vari-

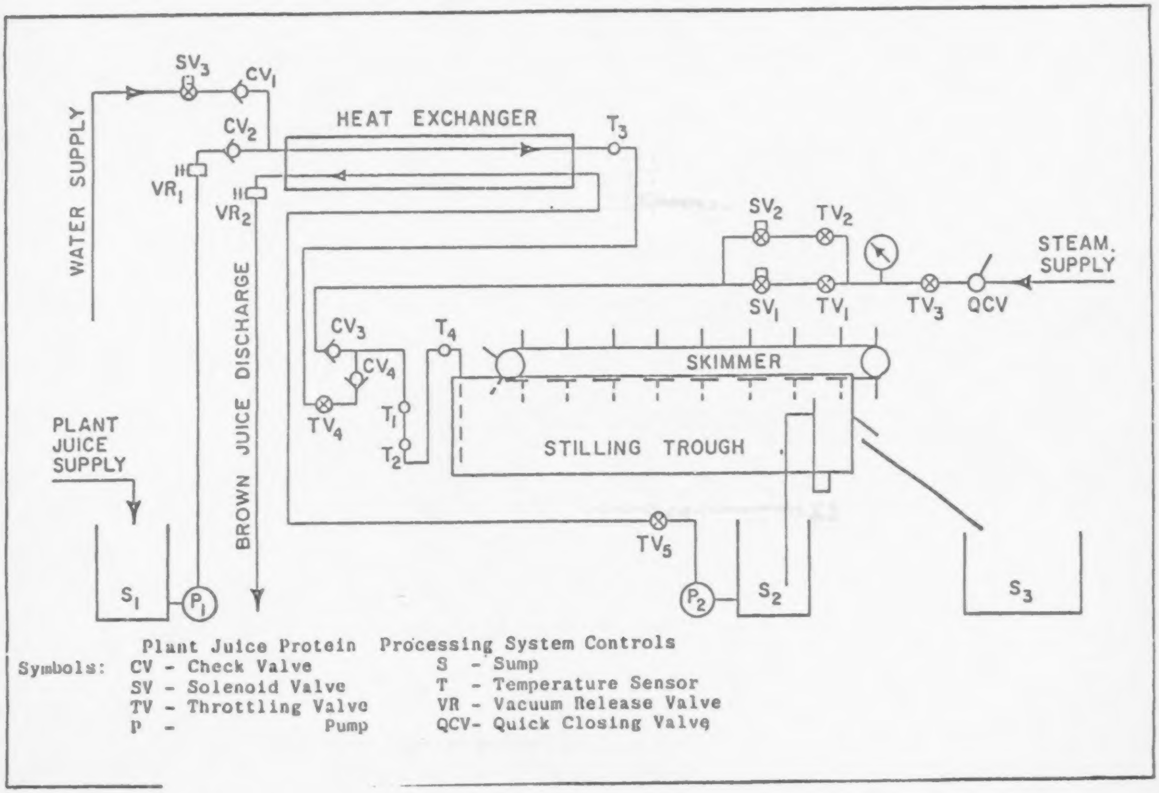
Table 7.—Separation Methods of LPC From Green Juice

REEN JUICE

	Treatment	Fractions	Reference
HEATING	not measured	green and white	Rouelle, 1773
	80°-84° C	green	Pirie, 1971
	60°and 84°	green and white	Edwards et al., 197
	55°, 64°, 82°	green and two whites	Telek, 1979
ACID		green	Pirie, 1971
ORGANIC SOLVENTS	ethanol acetone	green	Huang, 1971
	n butanol	green	Allison, 1973 in Hove and Bailey, 1975
ANAEROBIC FERMENTATION		green	Stahman, 1978
FLOCCULANTS		green	Anelli et al., 1977 Knuckles, 1980

SOURCE: Compiled by Telek, 1983.

Figure 6.—Flotation Separator


WATER SUPPLY
SV3
CV1
CV2
HEAT EXCHANGER
T3
VR1
VR2
SV2
TV2
STEAM SUPPLY
SV1
TV1
TV3
QCV
BROWN JUICE DISCHARGE
CV3
CV4
T4
SKIMMER
TV4
T1
T2
STILLING TROUGH
PLANT JUICE SUPPLY
TV5
S1
P1
P2
S2
S3
Plant Juice Protein Processing System Controls
Symbols: CV - Check Valve
SV - Solenoid Valve
TV - Throttling Valve
P - Pump
S - Sump
T - Temperature Sensor
VR - Vacuum Release Valve
QCV- Quick Closing Valve

SOURCE: Straub, et al. (75).

able moving speed of 3.0 to 15.2 m/min. (fig. 7). The belt filter was fitted with a 0.25-m long x 0.5-m x 0.3-m tank to allow for flocculation of the juice protein. This provided an average 1- minute hold time for the heat treated juice prior to being spilled onto the traveling belt by a paddle wheel assembly which rotated at a rate of 20 rpm. There was an initial free drainage section on the belt. This was followed by a vaccuum box dewatering section. The material then was scraped off to pans by a spring-loaded doctor blade (fig. 8). The evaluation of this process showed that flotation provides good recovery. However, the protein concentrate was dilute; it was less than 12 percent solids. The filtration provided moderate levels of solids, but had poor recovery rates. Use of flotation as pretreatment to belt filtration provided improved recovery and moderate solid concentration. Mean solid levels of proteins separated by various methods are shown in table 8. The results using this relatively complex machinery are somewhat disappointing, and further refinement is needed. In an on-farm operation, such as hog raising where a wet product can be used, this solid level would be acceptable. The protein concentrate could be mixed with barley or cassava chips for immediate use or partly extruded and sun-dried for short duration storage.

LPC Extraction at Village Level

The most basic application of leaf protein fractionation is at the village level. The operation is simple. Production should be geared to consumption by farm animals to avoid preservation and storage problems. The system, using the pulper and press developed at Rothamsted Experiment Station, England, and purchased by donors, has been studied in Pakistan (66), India, and Sri Lanka.

In a rural resettlement of people from urban slums in Pakistan, a trial has been suggested to test-market LPC produced by this machinery for dairy

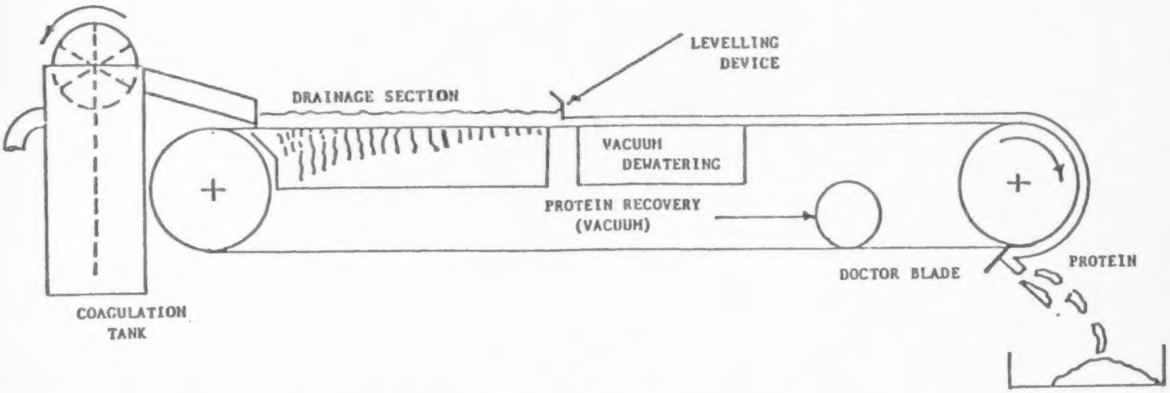
Table 8.—Mass Distributions, Suspended Solid Distribution and Resulting Protein Solid Levels for Flotation, Belt Filtration, and Combinations

	Separation Process*				
Mass Distribution (% of total)	Decant	Drainage	Dewatering	Recovery	Protein
Floatation & belt filtration	42.5	8.9^{a}	20.4	3.0	25.2^{a}
Floatation & belt drainage	42.5	8.9^{a}	-	-	48.6^{b}
Floatation	42.5	-	-	-	57.5^{c}
Belt filtration	-	46.1^{b}	23.1	3.3	27.7^{a}
Recoverable Solids (% of total(% absolute))					
Floatation & belt filtration	0.5(0.05)	0.7(0.37)	1.5(0.37)	5.7	91.6^{a}
Floatation & belt drainage	0.4(0.05)	0.6(0.37)	-	-	99.1^{b}
Floatation	0.4(0.05)	0.6(0.37)	-	-	99.6^{b}
Belt filtration	-	1.1(0.15)	0.9(0.23)	5.5	92.5^{a}
Solid Content (%)					
Floatation & belt filtration	-	-	-	9.7	18.4^{a}
Floatation & belt drainage	-	-	-	-	12.4^{b}
Floatation	-	-	-	-	11.4^{b}
Belt filtration	-	-	-	10.5	20.5^{a}

* Differing superscripts indicate statistical difference of 95% C.L.

SOURCE: Straub, et al. (75).

Figure 7.—Belt Filtration



SOURCE: Straub, et al. (74).

Figure 8.—Belt Filtration

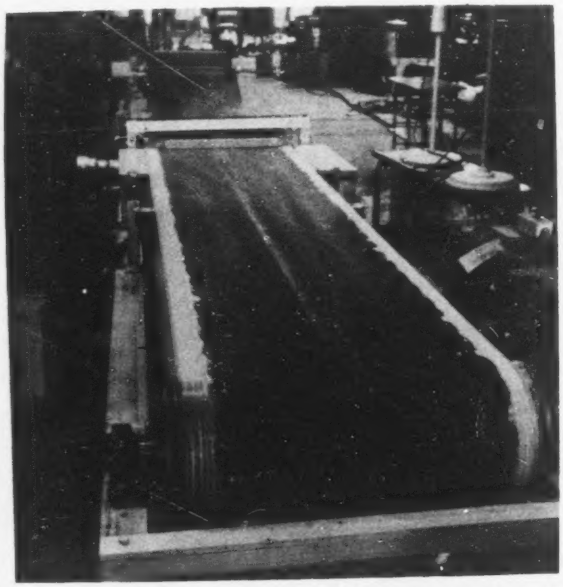


Photo credit: Courtesy of H. D. Bruhn and R. J. Koegel

cattle and green LPC for local sale. The labor force would be recruited from the resettled families under the supervision of trained personnel.

Indian and Pakistani scientists are cooperating in the leaf protein work. Dr. Shah of the Pakistan Council of Scientific and Industrial Research visited Mysore, Coimbatore, and Aurangabad to learn of the Indian progress in implementing village-level LPC production.

The work in Aurangabad, India, is the most relevant to practical application of any in progress. It attempts to establish a commercially viable LPC production unit at a village farm, using a simplified screw press that Pirie (62) has been developing for a number of years (fig. 9).

This press accomplishes both cell rupture and juice expression in a single press. A similar unit was built in the workshop of Marathwada University. The press is driven by a 3-HP motor. The juice is drained over a vibrating screen, then precipitated in a thermostatically controlled oil bath. The coagulum is filtered through cloth stockings (fig. 10). The locally constructed equipment could be scaled up according to need (18).

Joshi, et al. (42), reviewed the prospects and problems of leaf protein production on a small farm in Bidkin, an Indian village about 25 km from Aurangabad. The green protein concentrate made from alfalfa was used as a milk replacer for calves, as poultry feed, and as human food. The pressed crop was remixed with solubles and fed immediately to cows. They accepted the material willingly, however, they rejected it when offered it the next morning. Equipment and a dairy unit of 5 to 6 cows would cost at least $4,450 (Rs 35,500*), an excessive expenditure for a small farmer. Joshi suggested that, in the immediate future, both of the products of green crop fractionation be sold in the market. This project was supported by the Meals for Millions Foundation, and its economics were evaluated by Bray (13).

A flow chart for the process is shown in figure 11. After the crop is pulped, it is pressed to yield green juice and fiber. Heating the juice yielded 25

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*The exchange rate of the Indian rupee (Rs) is calculated at Rs 7.8 per $U.S.

Figure 9.—Simplified Screw Press

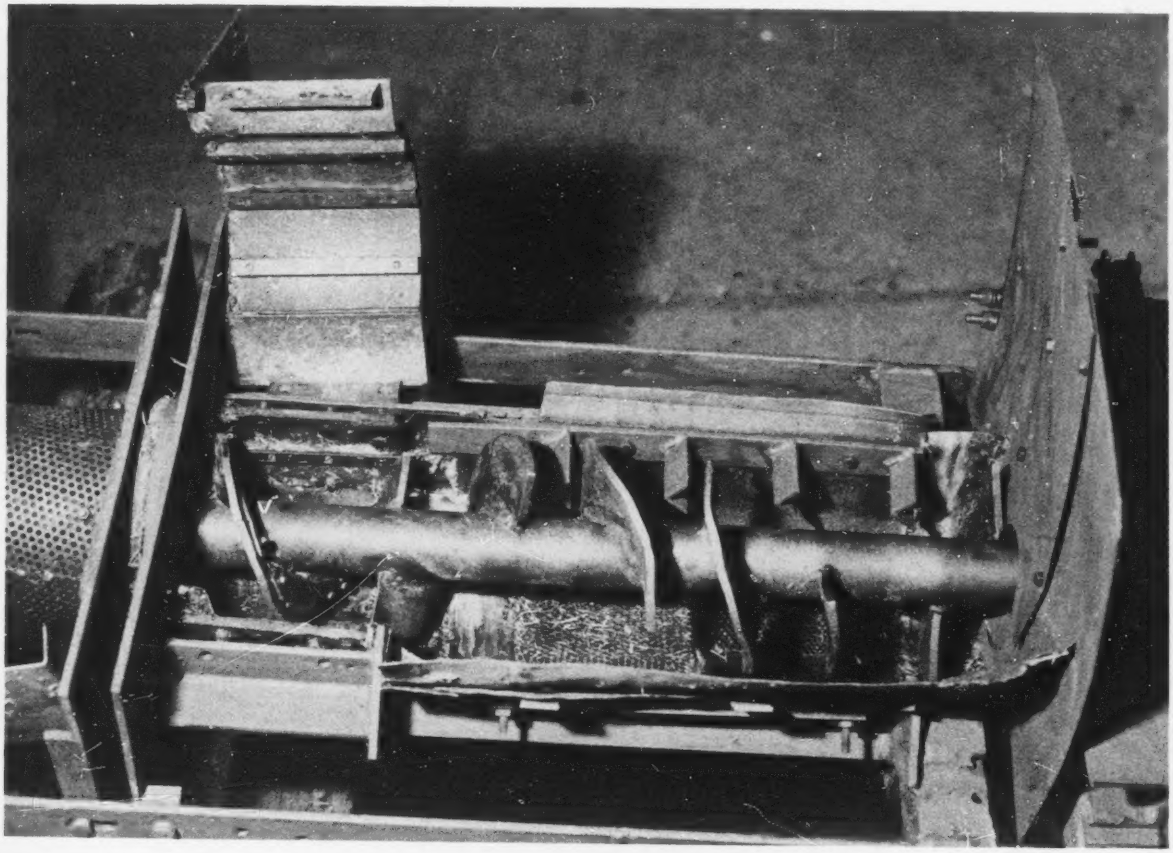
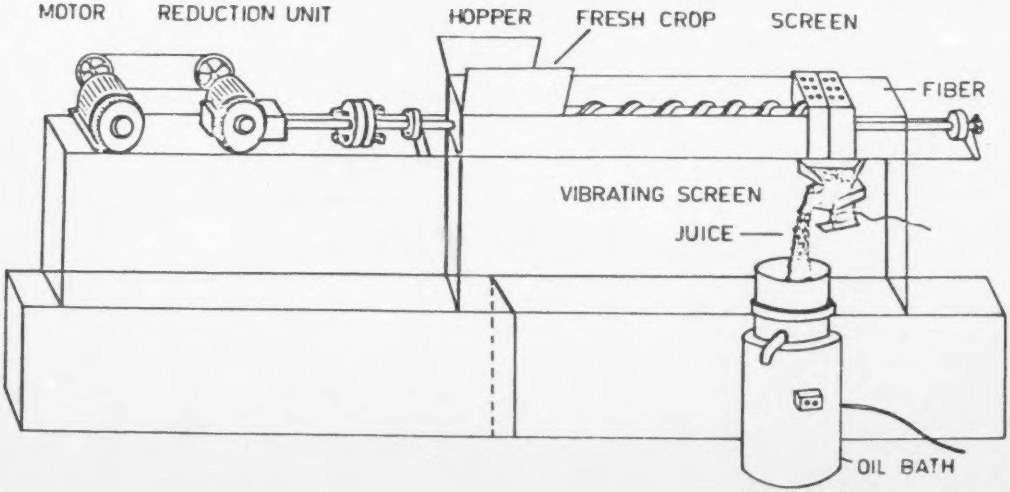


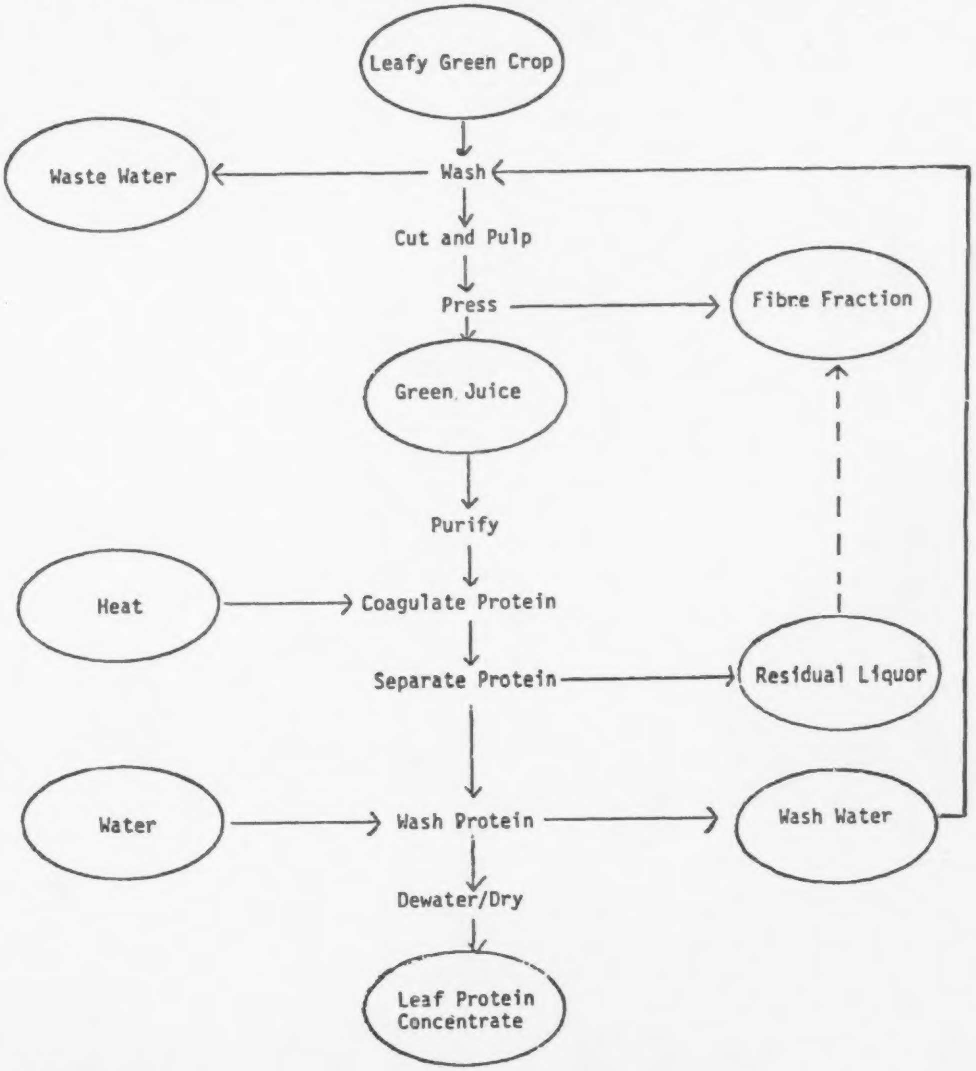
Photo credit: Courtesy of N. W. Pirie

Figure 10.—Screw Press Designed and Built in Aurangabad, India


MOTOR
REDUCTION UNIT
HOPPER
FRESH CROP
SCREEN
FIBER
VIBRATING SCREEN
JUICE
OIL BATH
COAGULUM

SOURCE: Courtesy of R. N. Joshi.

Figure 11.—Process Flow Chart of Leaf Protein Fractionation on Village Level in India


Leafy Green Crop
Waste Water
Wash
Cut and Pulp
Press
Fibre Fraction
Green Juice
Purify
Heat
Coagulate Protein
Separate Protein
Residual Liquor
Water
Wash Protein
Wash Water
Dewater/Dry
Leaf Protein Concentrate

SOURCE: Bray (13).

kg LPC from about 1 MT of freshly cut alfalfa. In a variation of this process, the pulped crop is extracted with the solubles from the protein precipitation phase, to yield an enriched fiber fraction for feeding ruminant animals. The leaf protein concentrate—containing 60 to 65 percent protein, 22 to 24 percent lipids, and carotenoids (pro-vitamin A)—could be consumed by people or nonruminant animals, or used as a milk replacer for calves. The input requirements for this process are indicated below.

Equipment Costs

The cost for both processes was calculated at about $3,200 (table 9).

Land

Since the extraction process requires about 1 MT of fresh alfalfa per day, the produce from about 2 ha would be needed to keep it operating continuously.

Table 9.—Equipment Costs for LPC Preparation on Village Level in India

Wash Tank	Rs 1500
Cutter	1540
Pulper	5500
Dewatering press	4500
Juice pump	1160
Liquid Cyclone	350
Waste Receiver	80
Holding Tank	160
Heater/Coagulator	1700
Curd Filter	100
Beam Press	900
Holding Tank	320
Mixing/Wash Tanks	160
Beam Press	900
Total Cost	Rs 18870 ($2,359.)
Installation 25%	4720
Contingency 10%	1890
	Rs 25480 ($3,185.)

SOURCE: Bray (13).

Crop Cost and Income

Current costs for alfalfa vary widely. With an expected yield of about 100 MT of fresh alfalfa/ha/yr, a farmer would receive $1,600, an income higher than he would get raising other crops.

Labor Requirements and Salaries

For an 8-hr day, the salary of the supervisor is $1.50, $0.99 for operators, and $0.75 for helpers.

Electric Power

The power required is 5.6 kW for pulping and 6.75 kW for pressing at $0.034 per kWh.

Fuel

The fuel is low quality coal that would cost about $0.002/kg LPC. The production cost per kg LPC is summarized in table 10.

Suggested retail price for 1 kg LPC would range

Table 10.—Leaf Protein Production Cost Summary at Village Level in India

	Process 1 (Pressing)
Raw material (net cost)	Rs 1.02/kg LPC
Labor and supervision	1.72
Power	0.58
Fuel	0.13
Maintenance	0.66
Supplies, etc.	0.29
	Rs 4.40 = 55¢
Depreciation	0.91
Interest expense	0.60
Other fixed charges	0.25
Total fixed costs	Rs 1.76 = 22¢
Total production cost	Rs 6.16/kg LPC = 77¢

SOURCE: Bray (13).

from $1.19 (Process 2) to $0.79 (Process 1). Leaf protein probably would be incorporated into a final food product, then sold. For example, in the Coimbatore feeding program, LPC was mixed with cassava flour and sugar and fed to children as a soft sweet mixture called a laddu. If a similar product containing leaf nutrient concentrate were to be sold in the market, it could be priced at $0.50 per kg. For only $0.025 to $0.03 per day, a child could obtain 50 percent of his daily protein, iron, and calcium and 100 percent of his vitamin A from such a product.

Conclusions

The following conclusions are drawn from this study (13):

1. A green crop fractionation/leaf protein unit could be easily operated in a village.
2. The cost of the equipment is low enough to be affordable by village cooperatives.
3. On a nutritional basis, leaf protein would be much less expensive than most of the protein from grain legumes consumed in the area.
4. An LPC-containing product that would provide 50 percent of the daily protein requirement of a child would be affordable by the majority of the Indian poor.

In Coimbatore, Friesian, and Jersey cows are consuming the pressed crop, and in preschool nurseries children are getting the LPC in laddu, a food item developed by Dr. Devadas, which consists of a mixture of leaf protein with jaggery (a crude sugar made from the sap of a palm tree), cassava flour, pearl millet flour, and sesame seed molded into soft balls. It was fed to the children as a snack. The object of her research was to evaluate the nutritive value of LPC through feeding programs for 600 preschool children for a period of 3 years.

On-Farm Use of LPC

The basic principle of leaf protein fractionation is that some plants, mostly the Leguminosae, contain much higher levels of protein than are necessary for ruminant nutrition. This protein can be removed without negatively affecting the growth of animals. On the other hand, nonruminants are unable to digest high contents of cellulose and cannot consume the amount of dry matter required to satisfy their protein requirements. Using protein fractionation, plant material can be separated into one product suitable for nonruminants and another suitable for ruminants. Experimental proof indicates that the process can double meat production in a given area (35).

The concept of on-farm use of leaf protein fractionation is that a weather-independent system can be devised in which the processing takes place on a farm and at least one of the products is used at the production site. The ideal situation would be a combined dairy and hog production farm using all of the products grown onsite, thus reducing transportation expenses, storage costs, and spoilage. This approach has been researched in Britain, Australia, and the United States.

The research team of the University of Wisconsin, under the leadership of Professor Bruhn, contributed the most in developing new concepts in machinery designs for this system (14). Research at the University of Wisconsin at Madison has concentrated on development of a weather-independent, on-farm forage harvesting system using a protein fractionation process. After harvesting, the main product is pressed forage, which can be preserved directly as silage. The prime objective is a quick reduction in the moisture content of the fresh forage from approximately 80 to 65 percent, a desirable moisture concentration for proper fermentation in a silo (31). By this process, field losses can be minimized to about 2 percent, a reduction from 32 percent or higher when the crop is preserved as baled hay. The pressed residue contains 50 to 80 percent of the dry matter of the original green crop. It retains 70 to 80 percent of its original protein content, which is substantially higher than that of sun-dried hays.

Use of Pressed Residue

Use of the pressed residue is the key factor in leaf protein fractionation. The maceration will make the fibers more digestible by ruminants. In sheep feeding trials, the pressed crop from either alfalfa or ryegrass was equally effective when fed freshly pressed or as silage (80,81). In steers fed a perennial ryegrass and Italian ryegrass mixture, the mean intake of whole and pressed crops was equal, and there was no significant difference in weight gain (40). The liveweight gains in cattle fed the pressed crop of perennial ryegrass were found to be significantly higher than those of cattle grazed on whole ryegrass *ad libitum* (35). Other research concluded that pressed residual can be fed directly to ruminants with as good results as the original nonfractionated plant (59).

Use of the Juice

The DM content of the green juice is low (8 to 10 percent). The isolation of green protein is an expensive process. The most economical use would be to feed it directly to hogs to minimize storage and preservation expenses. The green juice contains proteins, carbohydrates, and lipids. Enzymes present in juice degrade proteins rapidly, especially during warm days (69), and the soluble carbohydrate fraction ferments in 24 hours (4). Therefore, the process must be geared to the feeding time of the animals. Houseman and Connell (34) effectively replaced separated LPC and conventional seed proteins and dried LPCs by direct feeding of grass juice.

According to Braude, et al. (11), grass and alfalfa juice can replace half of the protein supplement (soybean or fish meal) in the feed of growing pigs. However, feeding experiments carried out in Wisconsin gave disappointing results. Pigs did not consume alfalfa juice even when their drinking water was withheld.

The most economical method for isolating proteins from green juice would be by anaerobic fermentation (1,49,72). Bacteria normally present on leaves fermented juice samples of many different plants (alfalfa; corn; oats; pangola, elephant, brome, and sudan grasses) in sealed containers. The initial pH of 5.5 to 6.0 dropped to 4.5 after 48-hour fermentation. Amino acid analyses of the fermented and spray-dried juice protein showed that it contained 40 percent more cystine and 12 percent more methionine. The protein yield was 11 percent lower than that prepared by heat precipitation. However, pigs' acceptance of feed containing the fermented product, especially in high proportions, was always low. An important need exists for animal nutritionists to convert the fermented LPC product into a palatable swine feed.

Industrial Production of LPC

In contrast to the village use concept stressed for LPC research, a serious investigation of process development for commercial LPC production was initiated in 1967 at the Western Regional Research Center of USDA in Berkeley, California. A large number of papers have been published on every phase, including use of the different products. A highly mechanized process evolved which is covered by several patents (8,10). Several reviews describe the development of the Pro-Xan process, the commercial production method for obtaining leaf protein concentrate from alfalfa (22,23,52). Figure 12 describes the flow sheet of the process.

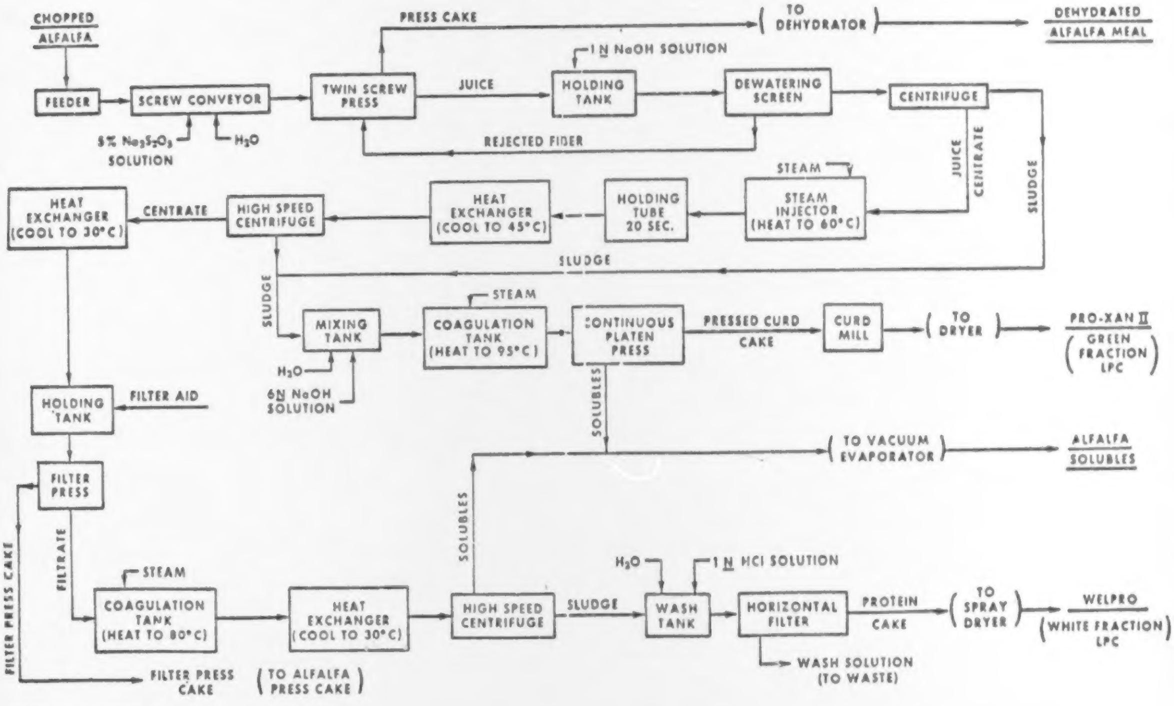
The original process has undergone several changes. Energy saving and pollution reduction were the main targets of process research; improved machinery was selected to accomplish these goals. The economies of producing Pro-Xan were studied by the USDA Economic Research Service and updated after major process changes (28,82).

The first commercial application of the Pro-Xan process was by France Lucerne, the largest producer of alfalfa dehydrators in Europe. The first pilot plant was constructed next to a dehydrator and produced 2 MT/day of green protein concentrate. In this process the pressed residue is added to the pelleted, dehydrated alfalfa. Also, the concentrated solubles are recycled to the pelleting operation. The success of the operation lies in the central location of the plant in Champagne, the largest alfalfa growing region in France; its well-organized sales operations; and the barge canal, rail, and highway connections available for shipping its products economically. A larger plant was completed in 1981 and 7,000 MT of green protein concentrate Pro-Xan are being produced yearly. France annually produces 900,000 MT of dehydrated alfalfa. Sixty percent of this is produced and marketed by France Lucerne in Champagne.

Alfa-Laval and France Lucerne agreed to sell two 600 MT/day production plants to the Soviet Union. The process is based on Pro-Xan technology modified by France Lucerne using alfalfa as plant material (3).

In conventional dehydration, alfalfa containing 20 to 22 percent dry matter is chopped, transported immediately to the plant, and dehydrated to 90 to

Figure 12.—The Pro-Xan Process used by the Valley Dehydrating Co.


CHOPPED ALFALFA
FEEDER
SCREW CONVEYOR
5% $Na_2S_2O_5$ SOLUTION
H_2O
PRESS CAKE
TWIN SCREW PRESS
TO DEHYDRATOR
DEHYDRATED ALFALFA MEAL
1 N NaOH SOLUTION
JUICE
HOLDING TANK
DEWATERING SCREEN
CENTRIFUGE
REJECTED FIBER
JUICE
CENTRATE
SLUDGE
STEAM
STEAM INJECTOR (HEAT TO 60°C)
HOLDING TUBE 20 SEC.
HEAT EXCHANGER (COOL TO 45°C)
HIGH SPEED CENTRIFUGE
CENTRATE
HEAT EXCHANGER (COOL TO 30°C)
SLUDGE
SLUDGE
MIXING TANK
H_2O
6N NaOH SOLUTION
STEAM
COAGULATION TANK (HEAT TO 95°C)
CONTINUOUS PLATEN PRESS
PRESSED CURD CAKE
CURD MILL
TO DRYER
PRO-XAN II
GREEN FRACTION LPC
HOLDING TANK
FILTER AID
SOLUBLES
TO VACUUM EVAPORATOR
ALFALFA SOLUBLES
FILTER PRESS
FILTRATE
FILTER PRESS CAKE
SOLUBLES
STEAM
COAGULATION TANK (HEAT TO 80°C)
HEAT EXCHANGER (COOL TO 30°C)
HIGH SPEED CENTRIFUGE
SLUDGE
H_2O
1 N HCl SOLUTION
WASH TANK
HORIZONTAL FILTER
PROTEIN CAKE
TO SPRAY DRYER
WELPRO
WHITE FRACTION LPC
WASH SOLUTION (TO WASTE)
FILTER PRESS CAKE
TO ALFALFA PRESS CAKE

SOURCE: Edwards, et al. (25).

92 percent dry matter in the rotary drier. This process generally produces a product higher in protein content than hay or silage produced from the same field, without the losses occurring during hay making and ensiling. Dehydration is less weather dependent than the other forage conservation techniques and is highly mechanized. The final dehydrated product is generally in the form of pellets which can be easily handled.

In the United States, the production of dehydrated alfalfa increased from 285 MT in 1944-45 to over 1,542,650 MT in 1969-70. In early 1970, a sudden decline in production occurred primarily due to competition of foreign producers. Later, the steady increase of energy cost and new air pollution standards decreased the profit margin in dehydrating. Many plants were closed and production fell below 1,181,818 MT.

Wet fractionation of freshly harvested crops can reduce the energy requirement because the pressed forage contains about 50 percent less water to be evaporated per MT of final produce. The latent heat from the dryers' exhaust gases was recycled for use in the evaporation processes, resulting in less air pollution.

The Valley Dehydrating Company (VDC), Sterling, Colo. (fig. 13) converted one of their existing plants to Pro-Xan production. The Department of Energy (DOE) supported the conversion as a means of demonstrating the efficient energy conservation possibilities in alfalfa dehydrators. With this funding, the research efforts of the USDA Western Regional Research Center, U.S. Department of Agriculture at Berkeley, Calif., could be realized in a new LPC production plant in the United States. The process equipment and operating parameters have been described in several publications (23,24).

The results of a detailed study of this company by Edwards, et al. (25), were published as a DOE report. The exceptionally high level of technology associated with this industry can be seen in table 11, which shows the considerable cost investment for conversion of a conventional 18 MT/hr dehydration plant to a 36 MT/hr Pro-Xan plant. Because of this high investment, it would be prohibitive to construct a similar factory in the humid tropics without previous extensive studies of available plant material at the on-farm level.

During the experimental period, the plant operated at 13.6 to 21.8 MT/hr, and produced an average

Figure 13.—Aerial View of the Valley Dehydrating Co., Sterling, Colo.

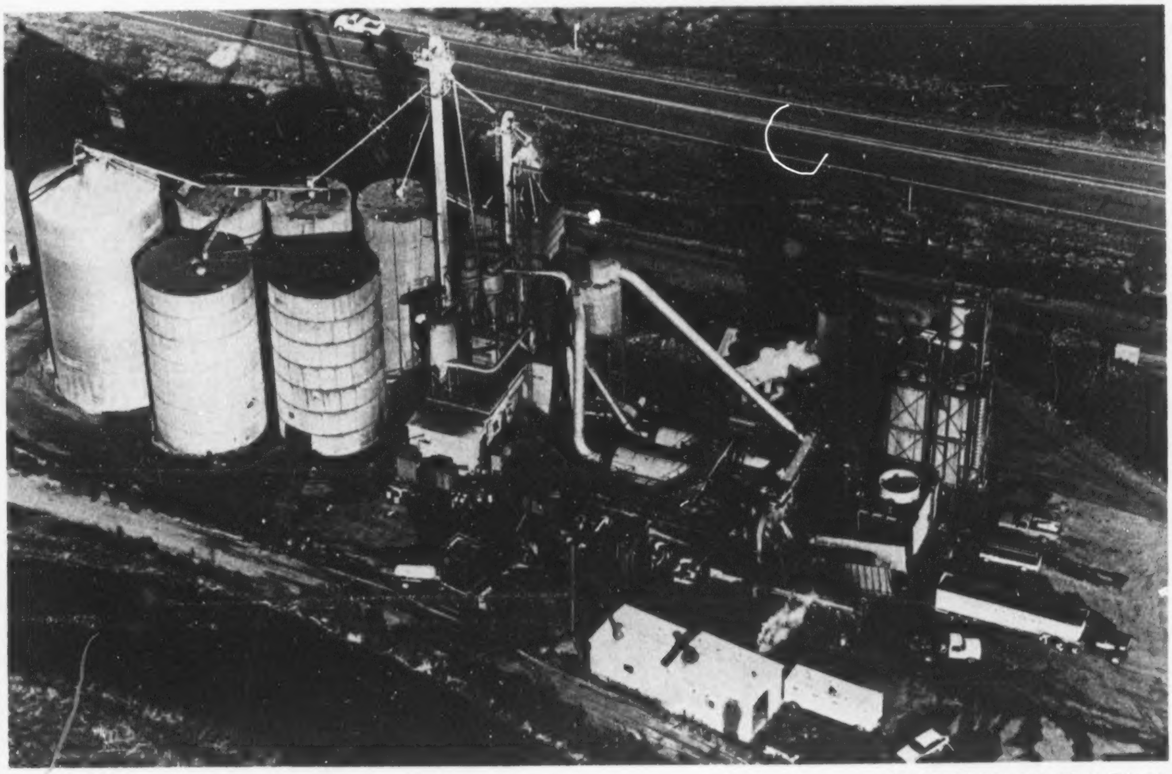


Photo credit: Courtesy of R. H. Edwards

LPC yield of 12.8 percent (dry basis). The VDC plant consumed 25 percent less total energy. Based on the experience at VDC, future LPC plants are projected to reduce overall energy consumption by 35 percent. The VDC products have been marketed readily; the press cake has been sold to cattle feeders at a price equivalent to dehydrated alfalfa, and the LPC to a broiler producer at prices varying from $391 to $530/MT. Animal performance trials using VDC produced products were highly satisfactory. Projected current cost of a new LPC plant processing 36 MT of chopped alfalfa per hour is $4.7 million (table 12); the cost of converting an existing 18 MT/hr dehydration plant to a 36 MT/hr LPC plant is estimated at $3.6 million. The calculated rate of return on investment for the new plant was 12.0, 26.2, and 40.4 percent for operating seasons of 130, 180, and 230 days, respectively (table 13).

The Vepex process was the first large-scale direct production method for LPC. It was built as a separate industrial unit not associated with a dehydrating industry. Its primary purpose was to maximize production of plant protein both for the fodder industry and for human nutrition. The process can also use raw material other than alfalfa.

Another essential feature is use of the deproteinized brown juice (33). Some of the nitrogen compounds present in the green juice are not precipitated by heat treatment. The soluble N in the deproteinized residual brown juice can amount to 30 to 40 percent of the total N content in the green juice. This can be used as substrate for feed grade yeast production.

A flow sheet of the Vepex process is shown in figure 14. Vepex plants are located in Denmark and Hungary. The plant in Tamasi in southwest Hungary is temporarily closed to make energy-saving improvements.

In Britain, the BOCM-Silcock Co. studied the preparation of dry leaf protein concentrates on a pilot plant level with the aim of creating a system to provide reasonably priced protein for feed in the form of storable products. The dry matter and pressed crop had to be at least 14 percent, a limit set by the European Common Market (78). The flow

Table 11.—Basic Equipment Requirements for a Modified Pro-Xan Plant Processing 36.3 Mg (40 t) of Fresh Alfalfa Per Hour

Item	Specifications	No. req'd	Total Connected power, kW (hp)
Forage harvester/chopper	self-propelled, 12 ft header	4	1/
Truck	22 ton, tandem axle, 34 ft bed, diesel powered.	4	1/
Truck	3/4 ton pickup	2	1/
Truck scale	60 ton	1	-
Feeder	40 tons/hr	1	29.8 (40)
Wet grinder	10 tons/hr	4	298.4 (400)
Screw press	single screw, 20 tons/hr	4	179.0 (240)
Hydrasieve	6 ft wide	1	----
Steam injector	3 in. dia.	2	----
Centrifuge	decanter type, 80 gal/min.	2	85.8 (115)
Drier, Pro-Xan with recycle system	triple pass, 6,000 lb H_2O/hr	1	44.8 (60)
Pellet mill, Pro-Xan	1-1/2 tons/hr	1	30.6 (41)
Bucket elevator, Pro-Xan	1-1/2 tons/hr	1	1.5 (2)
Pellet cooler, Pro-Xan	1-1/2 tons/hr	1	11.7 (15-3/4)
Scalper screen, Pro-Xan	1-1/2 tons/hr	1	0.4 (1/2)
Inventory scale, Pro-Xan	1-1/2 tons/hr	1	----
Bucket elevator, Pro-Xan	1-1/2 tons/hr	1	1.5 (2)
Load-out bin, Pro-Xan	1280 cubic feet	2	----
Waste heat evaporator, (3 stage, 2 effect) with cooling tower	40,000 lb H_2O/hr	1	173.1 (232)
Drier, press cake with recycle system	30,000 lb H_2O; 185°F	1	122.3 (164)
Grinder, dried press cake	9 tons/hr	1	224.9 (301-1/2)
Bag filter, press cake	9 tons/hr	1	23.5 (31-1/2)
Pellet mill, press cake	9 tons/hr	1	233.1 (312-1/2)
Bucket elevator, press cake	9 tons/hr	1	2.2 (3)
Pellet cooler, press cake	9 tons/hr	1	30.6 (41)
Scalper screen, press cake	9 tons/hr	1	0.4 (1/2)
Inventory scale, press cake	9 tons/hr	1	23.5 (31-1/2)
Pneumatic transfer system, press cake	9 tons/hr	1	----
Load-out bin, press cake	3328 cubic feet	4	----
Boiler, with economizer	400 boiler horsepower	1	41.0 (55)
Air compressor	36 SCFM	1	7.5 (10)
Pumps 2/	various, to 200 gpm	6	31.7 (42-1/2)
Conveyors, wet product	various, to 40 tons/hr	12	55.6 (74-1/2)
Tanks, with agitators	various, to 10,000 gal.	6	3.4 (4-1/2)
Well	250 gal/min	1	14.9 (20)
Heat exchanger	600 sq. ft., shell and tube	1	----
Waste water treatment	unspecified	--	37.3 (50)
		Total	1708.5 (2290.25)

1/ Not applicable.
2/ Does not include pumps in evaporator installation.

SOURCE: Edwards, et al. (25).

Table 12.—Investment Costs for a Revised Pro-Xan Plant with a Capacity of 36.3 Mg (40 t) of Chopped Alfalfa Per Hour

Item	Investment Cost, dollars
Equipment, harvesting and hauling	504,400
Equipment, process plant	2,793,349
Buildings[2]	282,500
Land[3]	46,800
Engineering and installation cost[4]	1,117,340
Total	4,744,389

[1] Based on May 1982 prices.
[2] Buildings include space for all operations except long term bulk storage which is treated separately.
[3] Six acres
[4] Assumes 40 percent of cost of process plant equipment.

SOURCE: Edwards, et al. (25).

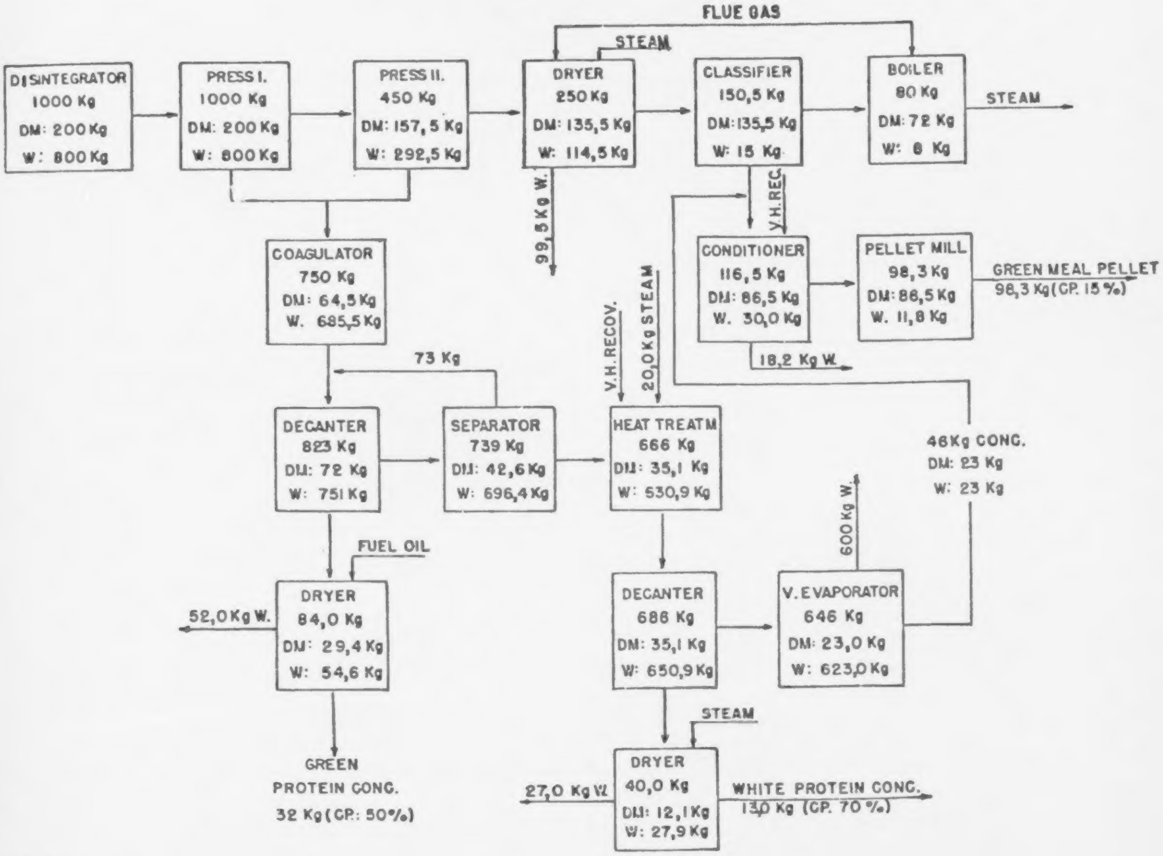
Table 13.—Annual Operating Costs, Revenues, and Return on Investment for the Revised Model Pro-Xan Plant

Item	Cost (dollars) at season length (days)		
	130	180	230
Annual Revenues			
Dehydrated press cake	2,645,261	3,662,669	4,680,078
Pro-Xan	1,803,023	2,496,494	3,189,964
Total Revenues	4,448,284	6,159,163	7,870,042
Annual Costs			
Alfalfa, raw material	766,480	1,061,280	1,356,080
Chemicals	60,126	83,251	106,377
Natural gas	516,663	715,377	914,094
Electricity	177,663	245,995	314,327
Fuel and oil	131,560	182,160	232,760
Maintenance and repairs	407,923	451,923	495,923
Labor	182,520	252,720	322,920
Administration	71,100	71,100	71,100
Property taxes	19,926	19,926	19,926
Insurance	54,676	54,676	54,676
Interest	499,491	537,027	574,563
Depreciation	336,317	336,317	336,317
Storage costs	143,162	198,225	253,287
Marketing costs	73,626	101,944	130,261
Transportation costs	436,304	604,113	771,922
Total costs	3,877,537	4,916,034	5,954,533
Total earnings	570,747	1,243,129	1,915,509
Total investment	4,744,389	4,744,389	4,744,389
Annual return on investment (%)	12.0	26.2	40.4

[1] Plant capacity 36.3 Mg (40 tons) chopped alfalfa (22 percent dry matter) per hour.

SOURCE: Edwards, et al. (25).

Figure 24.—Material Flow in Vepex Process


FLUE GAS
STEAM
DISINTEGRATOR 1000 Kg DM: 200 Kg W: 800 Kg
PRESS I. 1000 Kg DM: 200 Kg W: 800 Kg
PRESS II. 450 Kg DM: 157,5 Kg W: 292,5 Kg
DRYER 250 Kg DM: 135,5 Kg W: 114,5 Kg
CLASSIFIER 150,5 Kg DM: 135,5 Kg W: 15 Kg
BOILER 80 Kg DM: 72 Kg W: 8 Kg
STEAM
99,5 Kg W.
V.H.REC.
COAGULATOR 750 Kg DM: 64,5 Kg W. 685,5 Kg
CONDITIONER 116,5 Kg DM: 86,5 Kg W. 30,0 Kg
PELLET MILL 98,3 Kg DM: 86,5 Kg W. 11,8 Kg
GREEN MEAL PELLET 98,3 Kg (CP. 15 %)
V.H.RECOV.
20,0 Kg STEAM
18,2 Kg W.
73 Kg
DECANTER 823 Kg DM: 72 Kg W: 751 Kg
SEPARATOR 739 Kg DM: 42,6 Kg W: 696,4 Kg
HEAT TREATM 666 Kg DM: 35,1 Kg W: 630,9 Kg
46 Kg CONC. DM: 23 Kg W: 23 Kg
600 Kg W.
FUEL OIL
52,0 Kg W.
DRYER 84,0 Kg DM: 29,4 Kg W: 54,6 Kg
DECANTER 686 Kg DM: 35,1 Kg W: 650,9 Kg
V. EVAPORATOR 646 Kg DM: 23,0 Kg W: 623,0 Kg
STEAM
GREEN PROTEIN CONC. 32 Kg (CP.: 50%)
27,0 Kg W.
DRYER 40,0 Kg DM: 12,1 Kg W: 27,9 Kg
WHITE PROTEIN CONC. 13,0 Kg (CP. 70 %)

SOURCE: Koch (48).

sheet of this LP fractionation process is shown in figure 15.

When the full-scale plant was built, it required a growing area of 480 ha within an 8-km haulage radius. To operate at full capacity, the plant had anticipated producing lye-treated straw in the idle season. However, the straw feed was not acceptable in Britain, and the new plant was shut down after a brief interval of operation because the short production period made it inefficient to operate (79).

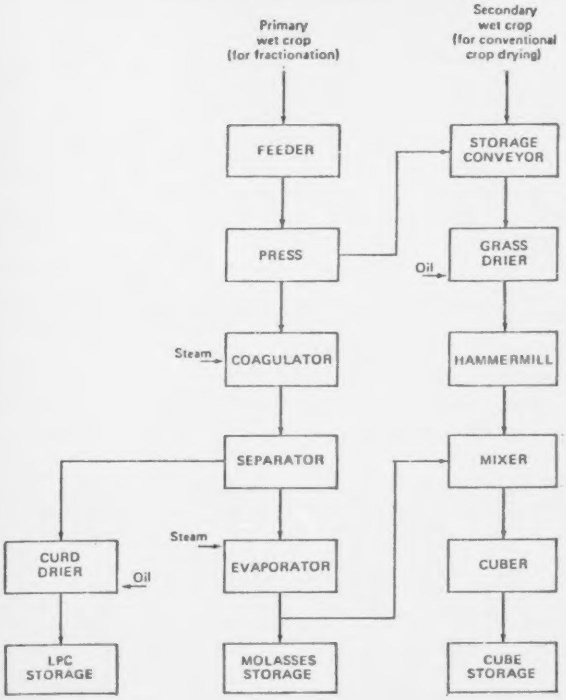
In New Zealand, Alex Harvey Industries, Ltd., in cooperation with the Ministry of Agriculture and Fisheries and the Broadlands Lucerne Company, is planning to establish a plant to produce a leaf protein concentrate with 47 to 50 percent crude protein content and high levels of xanthophyll and carotene pigments. This will be used for poultry feeding. A high fiber pellet for ruminant stock will also be produced. The plant will have a capacity of 10 MT/hr of green alfalfa and be operated by geothermal steam (67).

Two pilot plants managed by agricultural cooperatives began operation in Japan in 1981. Each processes 2.7 MT/hr of fresh herbage. One of them has facilities to separate LPC by centrifugation, condense green juice by reverse osmosis, condense brown juice by heating, cultivate yeast using brown juice, and make water from fibrous residue (58).

Preparation of Colorless Edible Proteins From Alfalfa

The processing of LPC to obtain a food-grade product was reviewed by Bray (12). Green LPC can be produced economically. However, some problems exist in human acceptance of protein concentrate prepared by heat precipitation at 82° C: its green color, grassy flavor, and low solubility.

Figure 15.—The BBOCM-Silcock Green Crop Fractionation Process



SOURCE: Thring (78).

A step in preparing improved protein in larger quantities by solvent extraction has been reported. Ineritei (38) found that freshly prepared coagulum could be decolorized with an acetone and isopropanol mixture. The treatment improves flavor and texture and gives a prolonged shelf life to the light cream-colored product by removing the lipids. The lipid distribution in green LPCs prepared from four tropical plants was analyzed by Nagy, et al. (55). The sale of lipid components, especially xanthophyll and B-carotene, and solvent recovery with solar power in the tropics could decrease the cost of this process.

Solvent extraction does little to improve the nutritional value of LPC. The tannin-damaged leaf protein concentrates are not or are only slightly improved nutritionally. Only a small amount of adsorbed tannins can be removed (17).

In the heat fractionation process, after isolation of the green protein at 55° C, in many plants two additional white protein fractions can be separated: one at 64° C and another at 82° C (77). The white protein fraction prepared from alfalfa is nutritious, with a protein efficiency ratio (PER) similar to that of casein (9).

The heat coagulated proteins are practically insoluble. It was suggested that they could be used in soups, gravies, cheese, and cookies (7). Food technologists for industrial application require certain functional properties for proteins. If leaf proteins could be processed to possess the desired properties, they would have wider use in the food industry.

Since solvent extraction of undried green protein has been costly and only partially effective and the white protein prepared by heat precipitation is insoluble, radically different and more complex procedures for producing soluble white and bland-tasting protein have been initiated.

In diafiltration, water is added to clarified alfalfa juice during ultrafiltration so that small molecular weight components can be washed through a membrane. On a laboratory scale, diafiltration, after a mild heat treatment and centrifugation for clarification, resulted in a freeze-dried product that was cream-colored and highly water soluble (46).

Pilot-scale ultrafilter units were tested by Knuckles, et al. (44) for concentrating and purifying soluble alfalfa leaf protein solutions after coagulating the protein at 60° C. Operating temperature was generally maintained at a low 10° C to avoid microbial growth and precipitation of the heat labile protein. The clarified alfalfa juice was concentrated to one-tenth of original volume, producing protein concentrates containing about 50 percent crude protein and 10 percent ash. Using diafiltration, water was added to the concentrated alfalfa juice until the permeate volume was 10 times the original sample volume. This method resulted in material containing 70 to 76 percent protein. Dried protein products were tan colored despite the removal of more than 86 percent of the ortho dihydroxy phenolic compounds.

The ultrafiltration systems tested by Knuckles and his coworkers cannot produce light cream-colored protein concentrates of greater than 90 percent purity. Because of their high cost and ineffectiveness, they are not viable methods for large-scale purification of alfalfa protein.

Flocculants are used to remove suspended solids from solution. Knuckles, et al. (47) reported their work with 54 commercial flocculants tested to improve the separation of the green chloroplastic protein fraction from alfalfa juice. With a 1-percent level of cationic flocculant, the chloroplastic fraction was separated by continuous high-speed centrifugation. Residual sediment was less than 0.5 percent; however, the processing rate was low (11.41/min). This technique also proved to be effective as pretreatment in membrane filtration. The treated juice yielded greater soluble protein content than the untreated control.

Knuckles and Kohler (43) prepared soluble leaf protein concentrates (light tan colored). According to the authors, these should be acceptable as a food source. However, no cost data is given. Gel filtration was previously used for fractionation of LPC by Fishman and Burdick (29) in characterization of protein of Coastal Bermuda grass proteins. The use of filter gels such as Sephadex is costly in even analytical processes. Freeze-drying is also a very expensive process because the special equipment is expensive and requires high energy input. Special proteins such as active enzymes may be prepared by this method for biochemical or medicinal purposes. Comparing quality and price, the proteins separated by gel filtration cannot compete with the Fraction I protein of tobacco, which can be prepared by crystallization and is water soluble. Dr. Wildman will discuss this unique protein in complete detail.

Environmental and Cultural Aspects

Nature and tradition have created richly variable cultures in tropical areas. It is difficult to design a general plan for a leaf protein extraction system for the entire tropical zone. It is evident that the whole system has to be geared to the natural and cultural local environment: the climate, physical location, soil fertility, and local cultural habits. Two-product use is a key to the viability of the LPC process. Ruminants must remain in the chain of protein production to use the pressed residue. In countries such as India, dairy animals or goats will be used on a smaller scale operation than that involving beef cattle in developed countries. The green LPC could be fed to humans or to calves as a milk replacement, saving milk for human consumption. In Islamic lands, cattle, lambs, goats, and rabbits could be fed the pressed residue, and chickens and ducks the green concentrate. In Latin America, the green juice could be fed to pigs and chickens, and the pressed residue to beef or dairy cattle.

The increasing protein shortage in the tropics cannot be alleviated effectively by village scale production of LPC, especially if it is used only for infant feeding. At the First International Conference on Leaf Protein Research held recently in Aurangabad, India, there were arguments regarding infant feeding trials between the representative of the bilateral and multilateral donor agencies and the recipient of grants for a children's feeding trial on one side and a highly respected local scientist on the other. The scientist claimed that "There is no doubt that leaf protein is good for protein and carotene nutrition. But its use in children feeding trials is considered unethical, purposeless, and unscientific. It is argued that the scope of the pigmented leaf protein in food is limited to the individual family or to communities of no social and economic disparities. Its production and use as a means for overcoming the protein and carotene deficiency in human nutrition is not a practical proposition" (70).

Advocates of infant feeding claim that infants respond favorably to feeding formulas containing alfalfa LPC. This claim could be contested. A protein-depleted infant would respond rapidly to any proteinous feeding. The effect of prolonged infant or child feeding of crude alfalfa green protein has not been properly evaluated. The following facts are disturbing. It is well documented that saponins of alfalfa impede the growth of chicks (16). Its tannin-phenol complexes are not digestible; their interaction with digesting enzymes of infants can be damaging. The biologically active coumestrol present in alfalfa was found in leaf protein concentrate (45). In the growth of children, the possibility of ill effects caused by the physiologically active ingredients of alfalfa green protein after prolonged feeding must be recognized. The dietetical value of the touted laddu, a product of high sugar content, also remains questionable. The large sum of research money spent did not produce basic data on possible long-term undesirable effects of the use of alfalfa LPC and did not reduce substantially the ever-increasing number of ill-fed children.

LPC as an emergency food for humans, as was suggested by Pirie for England during World War II, should be considered. Experimentally, it has proven to be nutritious; however, the author is against human use of LPC, especially that of alfalfa, because of incomplete testing and the possible presence of antinutritional factors. The small-scale production of LPC should not be rejected entirely. In extreme poverty, it could be incorporated as a protein source into native dishes. However, for human consumption of LPC, plants should be selected from local green leafy vegetables such as collard, mustard green, and other brassicas.

Pirie (63) suggested at the Belo Horizonte meeting in Brazil: "Except for infant feeding, nothing could be gained by extracting protein from leaves that can be eaten as green vegetables. The best way to use LP to improve the nutrition of unweaned infants is to give it to the mother rather than the infant. A broad-minded approach to botany is needed; the present occupation with alfalfa is unfortunate."

Advocates for LPC feeding for children cite the importance of carotenoids in diets of ill-fed children. LPC could supply these but carrots, tomatoes, and green leafy vegetables could also supply children with the needed carotene.

It is obvious that a farm's topography and size will be decisive factors in determining its ability to produce LPC. Small hamlets and subsistence farms will not be able to participate in LPC production. On small farms in the mountainous areas of the tropics, pods of winged beans and leafy vegetables such as collards, mustard greens, amaranthus, or even spinach could be additional sources of proteins and carotenes to supplement the family's daily consumption of beans and corn. Bananas or plantains, cassava, or yams are staples in such areas. It is difficult to believe that the wife of a struggling farmer in the Tropics will harvest leaves, pound them, filter the juice, and prepare a coagulum for food. Alternate sources of protein might be more acceptable to the low-income farmer. For example, the breeding of rabbits could be popularized on small farms. Harris, et al. (30), proved that dried tropical leaves, even those of cassava which are unfit for LPC production, supported the growth of rabbits and gave good results.

In a proper leaf protein preparation process, all products must be effectively used and not wasted. Since deproteinized juice cannot be used in small village units for yeast production, it should be used to irrigate fields. The fractionation process to white proteins would be a prolonged procedure with small yield for feeding trials. Similarly, the use of complicated purifications by ultrafiltration and gel filtration would be impractical.

The quality of life in rural areas of less developed countries has to be raised; however, a single, small industry like the bicycle-driven LPC production system used in India and involving a $3,000 investment will not substantially help alleviate the problems (fig. 16).

More moral and material support should be given to the plan of Joshi (41), which is a healthy transition to the on-farm use system. He suggested that in India LPC production could be incorporated into a small, cooperative dairy farm to improve animal husbandry for selected cows and to increase milk production. This would be practical. Dairy cooperatives are being used successfully in Europe, where the milk is collected for central processing and distribution.

Figure 16.—Screw Press Operated by Human Power in India

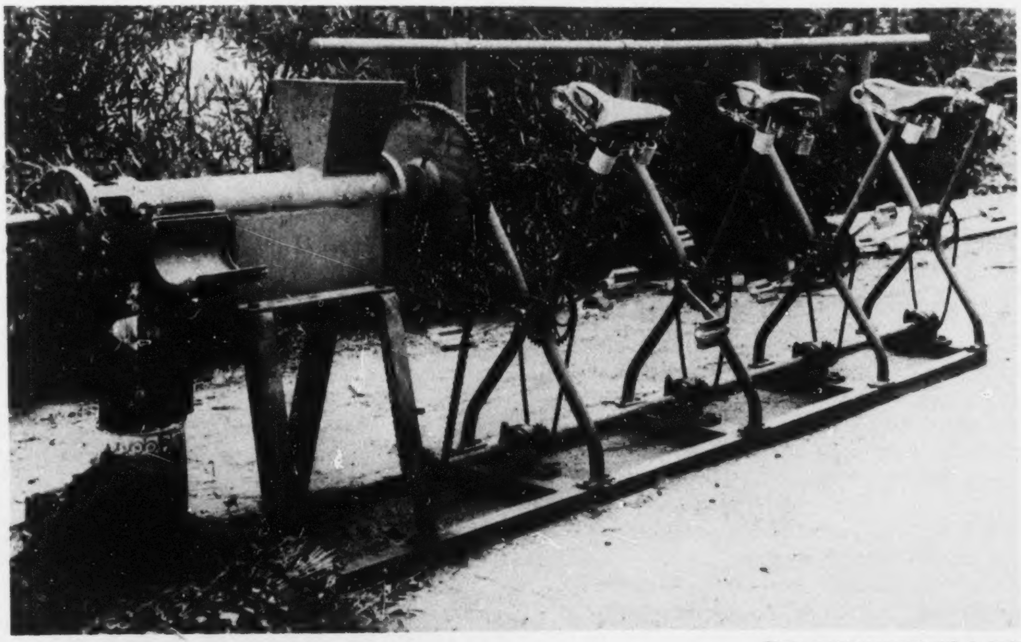


Photo credit: Courtesy of R. J. Joshi

The on-farm use system has been studied only with alfalfa and ryegrass. Using legumes, these model experiments could be duplicated in tropical countries, especially in Latin America where agricultural practices are well developed, land is available, and relatively simple technology could be successfully adapted to individual needs. The introduction of this type of system into areas of sugarcane production would reduce the acreage given to that crop, an economically sound decision. There is the possibility of substituting leaf protein for high protein feeds, such as soybean meal, in poultry and hog protein rations which are now imported into tropical areas.

As discussed in the on-farm use section, a production system of medium capacity is probably the level that will have a tangible effect on the protein resources within an area without disturbing its environment. There is no waste; the animal manure can be returned to the fields to improve the soil, and some of the pressed juice can be used for irrigation. The production facilities could process plant material contracted from neighboring farmers. A higher income level would result from more intense agriculture, which easily could be adapted to the existing conventional system. This size of agro-industry will not put a strain on electricity. The processing machinery could use small tractors as a source of power. It will not require a large amount of water, and only simple tools are needed for maintenance.

Research Needed

Leaf protein fractionation would increase the protein production of a given area universally. The basic farm equipment has been designed and properly evaluated, and existing machinery can process any fresh green crop with proper N level and extraction. The production level should be selected according to the needs of an ecosystem and modified according to the traditions and religious bias of the local population. Suitable plants should be studied in more detail, possibly using a medium-scale experiment at the production site. However, before expansion to the Pro-Xan type of operation can be contemplated, it is imperative that long-range studies be made of potential plant material at the on-farm use level.

USDA research centers and U.S. land-grant universities and tropical research centers in developed countries should have sufficient funds for the remaining basic and applied research needed for LPC extraction. An international cooperation between U.S. institutions and host institutions funded by AID should be developed for applying the research results in countries in the Western Hemisphere that would benefit from agricultural development based on LP extraction. A parallel program should enable scientists from host countries to learn the chemical and physical methods of production and quality control of raw material and finished products.

The host country scientists would offer the necessary data required for successful implementation. The following salient points must be carefully investigated by local scientists before a system and site are chosen:

1. Market research to determine need and acceptance of products
2. Availability of suitable land
3. Likelihood of undisturbed flow of plant material for processing.

The next phase of investigation should be nutritional evaluation of LPC products with large and small animals: cattle, milk cows, goats, rabbits, pigs, and chickens. The preparation of proper feed mixes should not be neglected. It is not sufficient to prepare a nutritionally balanced feed mixture; it should be readily acceptable by the animal and should have good keeping qualities.

Farm-level processing machinery has been well designed for disintegration and pressing. Only that used for the separation of green protein concentrate needs more investigation to obtain simpler and more effective equipment. An inexpensive basket centrifuge would probably be useful in this step of the process.

Well organized on-farm use of LPC could provide a thorough evaluation of tropical plants using medium-size technology and pave the way for the development of large-scale production of LPC—especially in tropical countries where advanced technology and sufficient amount of capital are available, such as Brazil, Puerto Rico, and Venezuela. After evaluation of plant sources on a farm scale, a commercial-size production facility is more likely to succeed.

While the capital requirements for large-scale production are high, the return on investment is also likely to be high because of the low labor costs and year-round operating season. The effect of the length of the operating season on return on investment is illustrated in table 13. The use of government subsidies to set up cooperative, commercial-scale plants might help initiate the new industry (26). Additional research funds should also be allocated to study low cost, more efficient extraction, dewatering, separation, and evaporation techniques that are suitable for large-scale LPC production from tropical plants studied previously and selected from intermediate-size studies.

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MOLLUSCICIDAL AND OTHER ECONOMIC POTENTIALS OF ENDOD*

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Abstract

Endod is the Ethiopian name for *Phytolacca dodecandra*, a full shrub closely related to the American pokeweed, *Phytolacca americana*. The young green leaves and shoots are edible protein sources after they are boiled and the water is discarded. An extract of saponin from *P. dodecandra* berries can be used as a molluscicide in the control of schistosomiasis and other snail-borne diseases. The berries have long been used as soap for washing clothes, and roots and leaves, although well-known for their toxicity, have been used as medicine for various ailments and as abortifacients. Recently, endod berries also have been discovered to possess potent spermicidal properties useful for birth control; aquatic insect larvicidal properties potentially useful in the control of mosquitoes and other water-breeding insects; trematodicidal properties for control of the larval stages of *Schistosoma* and *Fasciola* parasites; hirudinicidal properties for control of aquatic leeches; and fungicidal properties for the potential topical treatment of dermatophytes. Most of these studies are in experimental stages and need further support.

Extensive studies of molluscicidal properties of endod since 1964 suggest a new approach to the control of schistosomiasis and other snail-borne diseases by using locally produced endod on a community self-help basis. Commercially available chemical molluscicides are beyond the reach of developing countries because of their high cost, so endod or similar plant molluscicides that can be developed locally may be very valuable to poorer countries affected by these diseases. Endod's other newly discovered properties might provide additional economic incentives to develop it.

Careful agronomic studies of endod over a 5-year period led to the selection and experimental cultivation of 3 out of 65 strains collected from different ecological zones in Ethiopia. The three strains selected had high molluscicidal potency (two to three times more than previously used unselected strains), produced large yields of berries, and were highly resistant to insect pests. Application of new tissue culture techniques at the Plant Products Institute in Salt Lake City, Utah, is providing methods of cloning and cultivation for mass propagation of the plant. Endod is being used as a model plant by a biotechnology development program investigating in vitro biosynthesis of an active principle through a continuous calus-cell culture system. The cloned endod plantlets from Utah and the seeds of selected strains from Ethiopia are being grown experimentally in Ethiopia, Zambia, Swaziland, Brazil, and the Philippines.

The World Health Organization (WHO) Collaborative Centre for Traditional Medicine at the University of Illinois, Chicago, tested endod for mutagenic properties to determine its safety for widespread use. The results were negative, confirming an earlier study that endod has no mutagenic activity under the different experimental conditions used.

Encouraged by these developments, an International Workshop on Endod was convened in Lusaka, Zambia, in March 1983. The workshop reviewed all studies on this plant, identified gaps in knowledge, and developed specific projects that could be undertaken as collaborative ventures by a worldwide network of interested institutions and individuals.

Description of the Plant

Endod is the Ethiopian name for the soapberry plant *Phytolacca dodecandra* (L'Herit) (Synonyms: *P. abyssinica* Hoffin., *Pircunia abyssinica* Moq.), a member of the Phytolaccaceae family (fig. 1). The distribution of this plant is east, west, central, and southern Africa and parts of South America and Asia (1).

Endod has small berries which, when dried, powdered, and mixed in water yield a foaming detergent traditionally used in Ethiopia and elsewhere for washing clothes. In Ethiopia, endod exists as two main varieties, the more powerful *arabe* with pink berries and *ahiyo* with grey berries.

The plant is a rapidly growing climber with hanging branches. The plant's average height is 2 to 3 meters, although it can reach a height of up to 10 meters. Under favorable climatic conditions in Ethiopia, the plant bears fruit twice a year, in January and July.

Phytolacca dodecandra L'Herit and the closely related *Phytolacca americana* L., commonly known in the United States as pokeweed, long have been recognized for their varied uses. Different parts of the plant, including the leaves, fruit, and roots, are

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*The opinions expressed in this paper are those of the author and do not necessarily reflect those of the United Nations.

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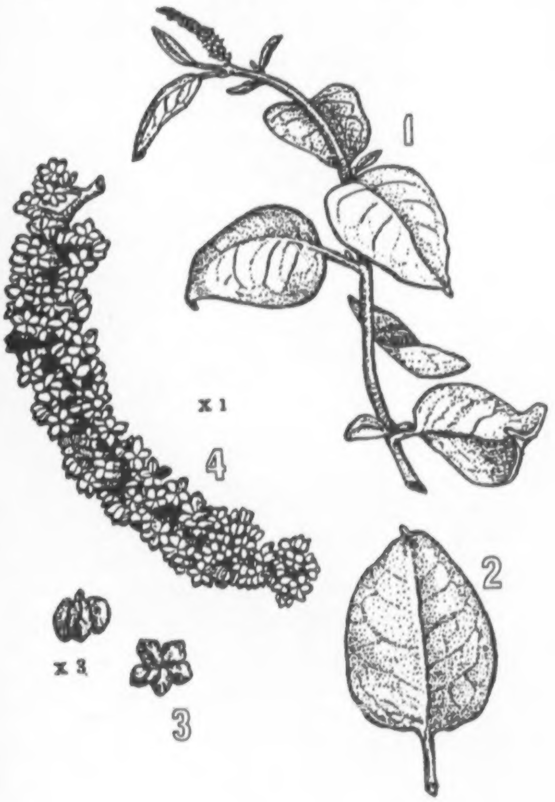

Figure 1.—Phytolacca dodecandra (Endod plant)

widely regarded for their emetic, purgative, taeniafugal, abortifacient, detergent, antisyphilitic, and other properties (2).

Discovery and Early Studies

In 1964, while doing an ecological study to determine the distribution of schistosome-transmitting snails in a small stream in Adwa, northern Ethiopia, large numbers of dead snails were found in areas immediately downstream of local people using endod to do their laundry. Live snails were abundant in areas further upstream and downstream from laundry sites. This led to subsequent studies of the molluscicidal property of this plant (3,4,5). The results obtained from these studies indicate that this or similar local plant products could be used as molluscicides to control schistosomiasis and other snail-borne diseases on a sustainable community self-help basis.

About 10 to 20 parts per million (ppm) of the sun-dried, ground endod berries diluted in water kill schistosome-host snails within hours of exposure. Endod's molluscicidal potency remains stable over a wide range of water acidity/alkalinity (pH) and with varying concentrations of organic and/or inorganic matter in the water, and is not significantly affected by solar ultraviolet light. In contrast, copper sulphate, the well known and widely used molluscicide, is adsorbed by organic and inorganic matter in treated bodies of water; sodium pentachlorophenate, another important molluscicide, is rapidly destroyed by ultraviolet light; and the widely used Shell product Frescon® is affected by the pH of the water in which it is applied (4,6).

Since the discovery of the molluscicidal properties of endod in 1964, more than 40 scientific articles have been published and several patents registered on different aspects of the plant (7,8,9). Unfortunately, because most of these publications are in journals with relatively limited distribution, such as the *Ethiopian Medical Journal*, the research results have not been accessible to many scientists and potential users in different parts of the world (5).*

Role of Molluscicides

The role molluscicides can play in effective control of schistosomiasis and other snail-borne diseases of humans and livestock has been well established. Numerous schistosomiasis control projects in Egypt, the Sudan, the Middle East, Japan, the Philippines, China, Brazil, and other countries have shown that snail control by molluscicides, either alone or in combination with other methods (e.g., chemotherapy, environmental measures, health education, etc.), can rapidly reduce or eliminate disease transmission. In recent years, there has been a marked change in snail control strategy from "blanket" or areawide treatment to seasonal and site-specific treatment. For more efficient, economical, and long-range results, focal mollusciciding efforts should be coupled with selected population chemotherapy and appropriate health education and community involvement. Such an integrated control strategy will continue to be the most effective approach until an appropriate vaccine against this disease is developed.

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*To make this information available in a single source, we have compiled the widely scattered reprints and publications on this plant and published them in a 522-page book along with a review of the status of endod research as of the publication date. Copies can be obtained free of charge from the authors (Aklilu Lemma, 145 Broadview Ave., New Rochelle, N.Y. 10804; or Dr. Donald Heyneman, Department of Epidemiology and International Health, University of California, San Francisco, Calif. 94143).

Comparison with Other Molluscicides

Several chemical molluscicides have been used for control of schistosomiasis and other snail-borne diseases over the last few decades. Among the most notable are copper sulphate and other copper salts which in the past have played major roles but largely have been discarded because of low efficiency and inactivation by various organic and inorganic matter in water. Another popular chemical molluscicide was sodiumpentachlorophenate, also discarded because of its irritant effect on human skin and rapid decomposition by solar ultraviolet light. The shell chemical product Frescon® (N-tritylmorpholine), known to be highly sensitive to variations in water pH, and the Japanese product *Yurimin* are no longer produced. The Bayer Co. product Bayluscide (niclosamide) is the best molluscicide commercially available and the only one recommended by WHO for widespread use. Because of the high cost of this product (more than $25,000 per metric ton (MT) in 1981), only a few developing countries are using it and on a limited scale with external financial assistance. The lack of market for molluscicides discourages private enterprise from searching and developing other products, including the organo-tin compounds, which have some promise for slow release application.

Plant Molluscicides

In recent years, as a consequence of the constraints to chemical molluscicidal use and of the encouraging results obtained from endod in Ethiopia, interest in plants with molluscicidal properties has increased. Thousands of plants have been screened for molluscicidal activities using a standard WHO procedure. The comparative potencies of endod and some of the leading chemical and plant molluscicides are shown in tables 1, 2, and 3.

Many plant molluscicides, such as from the fruits of *Sapindus saponaria, Swartzia madagascariensis, Balonites aegyptica,* and the bark of *Entada phaseoloides,* contain saponins. The roots of *Derris elliptica,* the pulp of *Agava susakaba,* and the leaves of *Schima argenta* have been reported in the literature to have molluscicidal properties. All of these are suspected to be harmful to the environment; there is long-established knowledge that they are potent fish poisons. Endod is the most exhaustively studied of the known plant molluscicides and provides a model for similar studies. *Croton tiglium, C. macrostachys, Jatropha curcas,* and *Ambrosia maritima* also deserve special consideration (10,11).

The seeds of two species of croton, *Croton tiglium* and *C. macrostachys,* that grow abundantly in the Philippines, India, and the Sudan, have high molluscicidal potencies. For an unknown reason, croton seeds are more active against *Bulinus* species of snails (transmitter of urinary schistosomiasis) than against *Biomphalaria* species (transmitter of intestinal schistosomiasis). A more serious drawback of croton is that it is carcinogenic and highly toxic to humans (12,13).

The seeds of *Jatropha curcas,* a plant that grows abundantly in the Philippines and produces seeds almost year-round, have a relatively high toxicity against *Oncomelania* snails and more moderate toxicity against *Bulinus* species (14,15). WHO is sponsoring studies to identify the active ingredient and determine the product's stability under various physical-chemical conditions and may undertake further field trials in the Philippines. The seeds and all other parts of the *Japtropha* plant showed no effect against *Lymnaea* snails, which transmit the economically important major animal disease, facioliasis (16). *Lymnaea* snails are major agricultural pests that multiply rapidly in rice paddies and destroy blue-green algae that are essential for nitrogen fixation (47). In an attempt to control these snails, scientists at the International Rice Research Institute in Los Banos, the Philippines, are introducing and testing endod, which is very potent against *Lymnaea's* adult and oval stages.

The leaves and flowering tops of the Egyptian plant, *Ambrosia maritima* (locally called damsissa), have some molluscicidal properties that have been studied for a long time. An infusion of the leaves at a concentration of 1,000 ppm kills planorbid snails in 24 hours (17); endod kills the same snails at less than 10 ppm in 24 hours. A positive feature of damsissa is that it seems to grow easily and reach maximum growth at the peak of schistosomiasis transmission in Egypt (11).

Monovicidal Nature of Endod

While some of the chemical molluscicides such as Bayluscide (niclosamide) are known to penetrate egg masses and kill unhatched snails, others such as *Endod* and *Frescon®* (N-tritylmorpholine) are

Table 1.—Comparative Potencies of Different Molluscicides

Molluscicide	Material Tested	Snails Tested	LC_{100} Exposure time	Authors
Chemical Molluscicides				
Bayluscide	Emulsion conc.	Biomphalaria spp.	0.3 ppm/24 hrs.	Günnert and Strufe, 1962(19
Frescon	16.5% Emulsion	Biomphalaria spp.	0.2-0.5 ppm/24 hrs.	Lugt, 1981 (18)
Copper sulphate	crystals	Biomphalaria spp.	3 ppm/24 hrs.	Günnert and Strufe, 1962(19
NaPcP	powder	Biomphalaria spp.	3 ppm/24 hrs.	Günnert and Strufe, 1962(19
Plant Molluscicides				
Endod	berries Water extract Butanol extract	Biomphalaria spp. Biomphalaria spp. Oncomelamia spp.	6.5ppm/24 hrs. 1.6ppm/24 hrs. 1.85 ppm/48 hrs.	Lugt, 1981 (18) Lugt, 1981 (18) Yasuraoka, 1971 (15)
Jatropha	seeds Water extract Butanol extract	Onchomelamia spp. Onchomelamia spp.	27-48 ppm/48 hrs.* 45 ppm/48 hrs.	Yasuraoka, 1976 (14)
Croton	seeds Water extract	Biomphalaria spp. Bulinus spp.	20 ppm/24 hrs.** 1 ppm/24 hrs.	Doffalla and Amin, 1976 (12)
Ambrosia	leaves and flowers in water	Biomphalaria spp.	1,000 ppm/24 hrs.	El-Sawy et al, 1981 (17)

[a] No action against *Lymnaea* and low activity against *Bulinus* spp. (16).
[b] No activity found against *Biomphalaria* by Lugt, 1981 (18).

Table 2.—Effects of Various Molluscicides on the Egg and Different Sizes of *Bromphalaria globrata* Expressed as 24-Hour LC_{90} (ppm.)[a]

Molluscicides	Eggs	Small (1-3 mm. diam.)	Large (10-15 mm. diamm.)
Endod**	100.00	4.70	3.00
Bayluscide	0.20	0.20	0.26
Frescon	40.00	0.20	0.21
Copper sulphate	4.00	0.70	0.50
Pentaclorophenol	1.00	0.65	1.00

[a] Adopted from Lemma and Yau (20).

[b] Endod is active against *Lymnaea* eggs at concentrations of 3-5 ppm in 24 hours. See text for possible explanation.

Table 3.—Molluscicidal Potency of Butanol Extract of Endod Against Various Species of Snails[a]

Snail Species (adults)	24-hr. LC_{90} (ppm.)	Investigators
Biomphalaria glabrata (NIH)	3.0 ± 0.25	Lemma *et al.*, 1972
Biomphalaria glabrata (Brazil)	2.3 ± 0.25	Paulini, 1971
Biomphalaria alexandrina (Egypt)	3.0 ± 0.25	Heynemann and Limm, 1971 Lemma *et al.*, 1972
Biomphalaria pfeifferi (Ethiopia)	2.8 ± 0.25	Yohannes *et al.*, 1970
Bulinus truncatus (Egypt)	3.4 ± 0.25	Lemma *et al.*, 1972
Bulinus truncatus (Ethiopia)	1.4 ± 0.25	Yohannes *et al.*, 1970
Lymnaea natalensis (Ethiopia)	2.8 ± 0.25	Yohannes *et al.*, 1970
Oncomelania nosophora (Japan)	1.6 ± 0.25	Wagner, 1971 Yasuraoka, 1971

[a] Adopted from Lemma and Yau (20).

known to be nonovicidal at molluscicidal concentrations. This has often been cited as a disadvantage of endod (table 2). This was particularly valid in the earlier days when "blanket" treatment or areawide application of molluscicides was the recommended procedure for controlling snails. Under those conditions, unless the molluscicide had ovicidal properties, repeated applications were necessary to kill the young snails hatched from unaffected eggs.

However, recent field studies in Egypt, the Sudan, Brazil, and St. Lucia indicate that the ovicidal property of a molluscicide may not provide the advantage attributed to it earlier. Repeated molluscicididing of such water bodies is necessary because treated areas are rapidly repopulated by snails from untreated parts of rivers or irrigation canals, even areas treated with the highly ovicidal Bayluscide. Under these circumstances, the ovicidal property, or the lack of it, may not be a significant advantage because the molluscicide has to be applied repeatedly on a regular basis.

In an attempt to determine whether endod was nonovicidal to only certain species of snails, eggs of different species of *Biomphalaria*, *Bulinus*, and *Lymnaea* snails were tested at the Harvard School of Public Health. Whereas 100 ppm or more were needed to kill *Biomphalaria* and *Bulinus* eggs in 24 hours of exposure, 3 to 5 ppm killed all *Lymnaea* eggs. These findings were further substantiated in field trials with endod in Puerto Rico where *Lymnaea*, *Marisa*, and *Physa* eggs and adult snails were destroyed by a concentration of about 5 ppm in 24 hours (5).

WHO Workshop on Plant Molluscicides

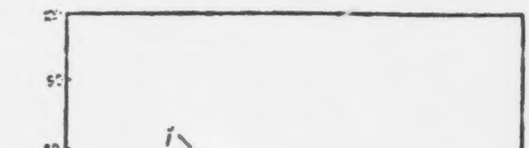
In response to the growing interest in molluscicides of plant origin, the scientific working group of schistosomiasis of the UNDP/World Bank/WHO special program of research and training on tropical diseases convened a workshop on plant molluscicides in Geneva, Switzerland, from January 31 to February 2, 1983. The workshop evaluated and recommended some specific actions for developing plant molluscicides. It recognized *Phytolacca dodecandra* (endod) as the most promising plant molluscicide studied to date. Subsequently, an international scientific workshop on endod was convened in Lusaka, Zambia, in March 1983. This workshop reviewed all past and present work on endod and recommended future areas for collaborative work among developing countries and among developing and developed countries.

Field Evaluation of Endod

In a 5-year schistosomiasis pilot control study with endod in Adwa, Ethiopia, the prevalence of *S. mansoni* in children between the ages of 1 to 6 was reduced from 50 percent at the start of the project (1969) to 7 percent after continuous control for 5 years (1973). The incidence of disease throughout the population in Adwa (17,000) dropped from 63 to 34 percent in 5 years. This included many incurable chronic cases in older individuals. This was achieved by systematic application of crude ground endod berries collected from the immediate neighborhood of Adwa (21).

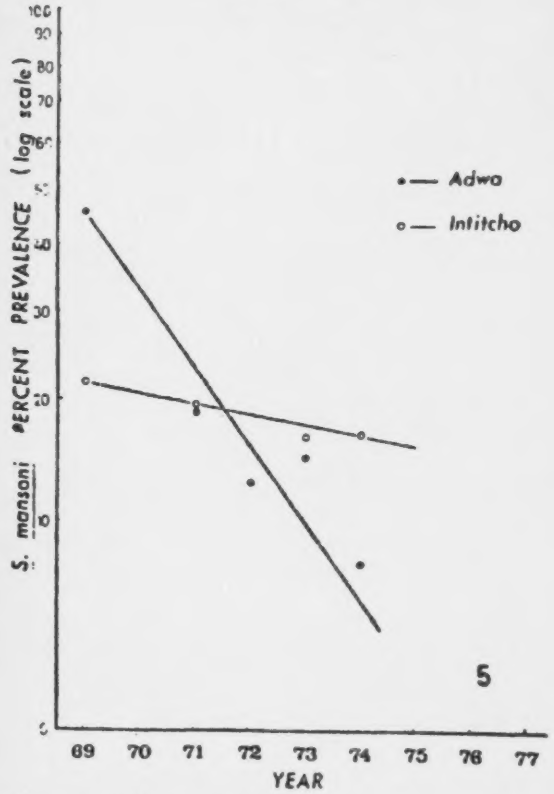
Annual disease surveys during the study showed a progressive reduction both in prevalence and new reports of the disease in Adwa, while these figures remained almost constant in the untreated nearby village of Inticho, suggesting that the action primarily was due to endod applications reducing the snail population (figs. 2 and 3). Ecological observations

Figure 2.—Prevalence Rates of *Schistosoma mansoni* in Adwa Before and After Control Measures by Application of Endod



SOURCE: Adapted from Lemma, et al. (21).

Figure 3.—Prevalence of *Schistosoma mansomi* in Children 1-6 Years Old in Adwa and in the Control Area of Intitcho



SOURCE: Adapted from Lemma, et al. (21).

during these 5 years indicated that endod had no obvious adverse effects on the microflora and fauna of treated streams (21).

Significance of Application of Schistosomiasis Control

Schistosomiasis is one of the most important and rapidly spreading parasitic diseases of mankind, a growing threat to large-scale irrigated agriculture and hydroelectric power development schemes in many tropical and subtropical parts of Africa, the Middle East, the Far East, and many parts of South America. An estimated 200 million to 300 million people are affected by this debilitating disease, and another 300 million to 400 million potentially are exposed to it.

The spread of schistosomiasis is a tragic example of man's actions. Well intended irrigation and other water-related development projects in tropical countries often have created new breeding habitats for the snails that transmit this disease. Infected and noninfected people working in such areas often must drink from, bathe in, and labor in the same canals. Human wastes often are excreted, dumped, or washed into the same water, leading to the rapid spread of this disease, especially among highly vulnerable children.

Inasmuch as schistosomiasis is a social disease, its control poses a major social challenge. There seems to be no single method to control schistosomiasis effectively. Ideally, effective control should involve the combined uses of mass treatment of all infected people, snail control using molluscicides to interrupt disease transmission, health education, and improved standard of living.

In spite of recent promising developments, there still is no safe, effective, and affordable drug suitable for mass treatment. Treatment by drugs (containing toxic compounds) sometimes was more tortuous than the disease itself. An excellent new drug, Praziquantel, still is too expensive for mass use. However, even if an ideal drug were available and cured an individual, he or she probably would be reinfected as long as the source of infection remained uncontrolled. Unfortunately, health education and improved environmental sanitation are long-range measures, closely interwoven with general socioeconomic and educational structures of a community. They must rely on governmental policies, plans, and available resources to increase the standard of living of the affected population. Under present circumstances, the most effective and practical method of controlling schistosomiasis is through a combination of selective treatment of infected individuals and control of new transmission by killing the host snails at each proven site of infection.

Community Participation

One essential component of the Adwa project was active community participation. The provincial governor-general, the mayor of Adwa, and the Municipal Council all were involved throughout the duration of the program. Their roles in planning and executing the project were essential for its ultimate success. The budget for the 5-year pilot-control project was provided by the Adwa Municipal Council. The Council also provided necessary facilities and manpower, including a headquarters for the project and local staff to run the field work, collect endod from wild plants, or purchase endod from local markets where it is sold as soap (21).

Another major reason for community participation is to have the community, through its Municipal Council, continue the control program on completion of the 5-year experimental work. Involvement of the affected population in the control of the disease on a "community self-help" basis is critical to the long-term success of a program. Projects are all too often discontinued as soon as the outside team leaves.

Detergent and Foaming Properties

The detergent and foaming properties of endod have been tested (Shell Crane, pers. comm.) with a detergiometer and compared with other commercially available detergents in a preliminary trial at the Stanford Research Institute (SRI) in 1971. It was found to be an effective clothes cleaning agent. Further studies should find ways to make the extract serve as a supplement or substitute for other detergents. Endod has the advantages over some chemical detergents of being harmless to delicate fabrics (such as fine cotton, linen, and wool) and of leaving the clothes noncompressed. Further, it is biodegradable and its use has no apparent deleterious environmental effects. Experimental evidence suggests this as does its centuries of use in streams, but more research should be done in this area.

The high foaming property of endod could be modified for use in lightweight concrete and foam rubber. It may also be possible to use it as a dispersant in perfume manufacture. Limited preliminary studies indicate commercial potential, but a great deal more investment and study is needed.

Larvicidal Properties

Studies at Harvard University on the comparative toxicity of endod and other compounds on stream flora and fauna showed that mosquito larvae are particularly susceptible to the lethal effect of endod (22). This led to other investigations which demonstrated the susceptibility of larvae of the notorious black fly (*Simulium spp.*), which transmits river blindness, or onchocerciasis, and larvae of the domestic house fly, *Musca domestica* (23,24). Further development of endod as an insecticide for village use could have public health significance. Since snail and malaria-transmitting mosquitoes may breed in the same type of environment, control of snails with endod may have the added benefit of reducing mosquito populations.

Hirudinicidal Property

The aquatic leech, *Lymnatis nilotica*, a major animal pest of livestock in many tropical countries, is susceptible to endod (5). Endod has been used for centuries in Ethiopia to control this pest. This use should be improved for more effective protection of domestic animals against this debilitating ectoparasite.

Trematodicidal Property

Schistosome cercariae and other trematode larvae are highly susceptible to endod. Infected waters can be rendered safe for several days by application of small quantities of endod. The active ingredient can also be prepared in ointment form for application on exposed skin of workers in irrigation canals as a prophylaxis against cercarial penetration. This has been tried at SRI with some success using the tails of test mice coated with endod ointment and immersed in cercaria-containing water (20).

Spermicidal Properties

Systematic biological screening of the butanol extract of endod showed it to be an extremely active biological agent against human sperm, thus suggesting its possible use as a locally produced, vaginal foam birth control agent (9). Endod long has been known and is widely used as an abortifacient in traditional societies in Ethiopia and other parts of East Africa. Recent laboratory studies have shown it to cause strong uterine contractions (25). Intrauterine injection of small quantities of endod extract in pregnant mice causes sterile and apparently harmless abortion. In addition to preventing pregnancy, it may be useful as a "day after" pill (26).

Other Snail-Killing Properties

Endod is also effective against snails that transmit other important human and animal diseases besides schistosomiasis. Laboratory and field studies have indicated that *Lymnaea* spp. are extremely susceptible to endod. These are the snail hosts of important cattle and sheep liver fluke that cause fascioliasis. Spraying pastures with relatively low concentrations of endod will kill snails, eggs, and infective larvae of the parasites without affecting the animals or vegetation on which it is sprayed. In view of the worldwide distribution of fascioliasis, development of endod to control this disease could benefit not only developing but also developed countries.

Lymnaea snails, which multiply rapidly, reach a biomass of 1.5 MT/ha in some ricefields in the Philippines and graze heavily on blue-green algae that are carefully introduced and grown for nitrogen fixation in paddy fields (47). The International Rice Research Institute in Los Banos, the Philippines, is investigating the possibility of using endod to control these snails (P.A. Roger, pers. comm.).

Fungicidal Properties

Biological screening tests have revealed that endod has a selective toxicity to dermatophytes, the fungi that cause a variety of skin conditions, such as athlete's foot and ringworm. The possible use of endod for treatment of these diseases needs further investigation (27,45).

Toxicological Studies

One of the most important criterion for widespread use of any molluscicide is its safety to humans, animals using the treated bodies of water, and local flora and fauna. The possibility of long-term negative effects from using such compounds should also be determined. Preliminary studies on the toxicity of endod to a variety of animal and plant species and tests for carcinogenic properties have been undertaken (4,28). Some of these earlier tests have been recently reconfirmed at a WHO reference laboratory at the University of Illinois in Chicago (Norman Farnsworth, pers. comm.).

A comparative toxicity study in sheep and dogs, as representatives of large ruminant and monogastric animals, both domestic and wild, that might drink endod-treated water, has also been undertaken. Sheep force-fed with the water extract at a dose of 1 gm/kg body weight died within 96 hours, whereas a dose of 200 mg/kg body weight had no apparent effect on kidney and liver function tests done over a period of 4 days (29). Oral administration to dogs at a dose of about 100 to 200 mg/kg body weight caused vomiting within minutes. Intravenous injection at the dose of about 50 mg/kg body weight was lethal in less than 24 hours, but 8 mg/ml of blood did not show any significant changes (29). Thus, although endod is known to be hemolytic to red blood cells if injected intravenously, it generally is well tolerated by animals if administered orally. When taken orally by humans and monkeys, it immediately causes vomiting so most of the product fails to reach the intestine. The emetic property of the berries is so strong that SRI chemists considered using it to prevent possible overdose from potentially dangerous drugs such as sleeping pills.*

Continuous application of high concentrations of endod solution to economically important plants over long periods of time appears to act as a fertilizer, promoting more rapid growth of test plants compared with controls given only water (4).

As with other molluscicides (20,30), small fish and tadpoles are affected by endod at molluscicidal concentrations. However, edible fish rarely breed in the small streams and canals where disease snails normally breed; adult frogs instinctively jump out of treated waters; and large fish swim rapidly from endod-treated sites to avoid its irritant effects. Hence, the product does not appear to have a significant impact on these animal populations. Birds known to feed on berries of wild plants seem unaffected, as do waterbugs in treated streams. During the 5-year experimental period in Adwa, treated streams were monitored for possible toxicity of endod to representative species of the flora and fauna, and no apparent effects on the aquatic ecology were noted. There has been no apparent negative impact from endod use in rural communities where endod has been and still is being used for washing clothes.

Our studies have shown that the active principle in endod biodegrades rapidly. The lethal effects following endod application to streams, canals, or lakeshores persist for 24 to 48 hours, after which time endod's potency rapidly declines.

Endod berries have been used for washing clothes in streams and lakeshores in Ethiopia and other parts of Africa for centuries, with no apparent toxic effect. Also, in Ethiopia and elsewhere in Africa, high concentrations of the endod leaves, roots, or berries are taken orally for various medicinal purposes, such as for purging intestinal parasites and for abortion (2,25). If endod had any harmful effects, surely it would not have survived centuries of human use. As with all natural products used by local people, its dangers would have been recognized and the substance discarded.

These assumptions were in part tested through mutagenic studies done on *Phytolacca dodecandra* by Lemma and Aimes (1974) on in vitro assays using a *Salmonella typhimurium* strain that since has given possible false results in the presence of histidine, a material normally found in most plant extracts including endod. Since traces of histidine from endod could have interfered in those tests, the negative data obtained in the 1974 study were considered equivocal and new tests were undertaken by Dr. N. R. Farnsworth of the WHO Collaborating Centre for Traditional Medicine and College of Pharmacy, University of Illinois, Chicago, using strains of *Salmonella* that are not affected by histidine. The results were all negative, confirming that neither endod nor pokeweed, which was tested for comparison, have any mutagenic properties under the experimental conditions employed (Farnsworth, 1983, pers. comm.).

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*Since the active component in endod is a relatively large molecule, it is assumed that it may not be able to easily penetrate the walls of the gut and enter the bloodstream where it could cause much damage. Also, itsemetic properties in regurgitating animals may give it a built-in protective mechanism to safeguard against its possible harmful effects.

However, conclusive evidence of mutagenic tests and other chronic toxicity of endod or any other similar product should come from carefully designed long-range toxicity studies in different species of animals, rather than from tests in isolated in vitro cell systems. To this end, the author hopes that WHO and/or another concerned organization will finance such a long-range study on endod so that its widespread use in areas where it is most needed could be further promoted and effectively applied.

Chemical Studies

The endod plant provides material of special interest to organic chemists involved in saponin chemistry, partly because of the high percentage by weight of crude saponins in dried berries, and partly because of the chemical complexity of the materials. Most chemical work on endod until now has concentrated on the saponins of dried berries. Although this work has yielded interesting chemical findings and valuable biological discoveries, according to Parkhurst, it seems that this is only "the tip of the iceberg" in developing the chemical potential of endod (31).

Chromatographic separation of crude saponins in endod demonstrates the dozens of compounds present, of which only a few have been characterized. The nonsaponin fraction, amounting to 75 percent of the total weight of the dried berries, may be broken down into petroleum-soluble lipids, water-soluble sugars, starches, pectins and gums, and a water-insoluble fraction. Little is known about the chemistry or potential uses of these fractions. Abundant as the berries are, they represent a small fraction of the plant, the rest of which is ample material for future chemical study (35,36,37).

Valuable byproducts have been obtained through the development and refining of endod. The water-soluble fraction with sugars and various polysaccharides, produced in the isolation of crude endod saponins, remains to be studied. New pectins, starches, thickening agents, material for fermentation to alcohols, and sources of rare sugars with industrial importance all may be found in the plant material left after the berries are cropped. The water-insoluble fraction, also not yet investigated, may be useful as animal feed, a fuel, or a soil additive.

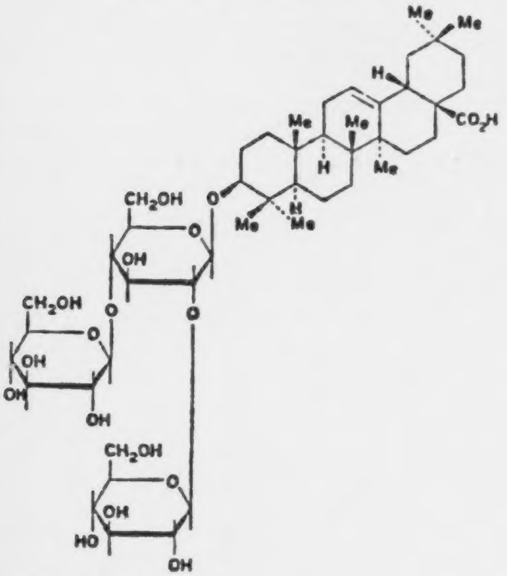
A green lipid material is obtained from the petroleum extraction of endod. While most of this material is composed of palmitic, oleic, and stearic acids, 12.5 percent consists of a nonsaponifiable, bright orange, waxy material containing squalene and a complex mixture of high molecular weight alcohols—i.e., phytosterols and/or triterpenols. As the value of endod saponins is established and production rises, large-scale development and additional uses for the saponin will follow and more byproducts should become available.

Chemical studies to isolate and identify the active principle in the endod berries have led to the discovery of a new compound, oleonolic acid glucoside, which Parkhurst, et al., have named *Lemmatoxin* (32,33,34) (fig. 4). Three different procedures have been developed in different laboratories to extract the active ingredient from endod berries. The first method, developed and patented by the Tropical Products Institute in London in 1971, was relatively complicated, based on methanol extraction followed by potassium hydroxide hydrolysis in two steps (7). In 1972, a simplified method involving single-step butanol extraction from an aqueous suspension of dried berries was developed and patented by SRI investigators in California (8,38). Both of these procedures give extracts effective at 2 to 4 ppm. However, both procedures have the disadvantage of depending on importing extraction solvents, thus demanding hard currency. This shortcoming was finally overcome by the third and perhaps most practical and promising extraction procedure which is based on fermentation techniques. It was discovered by the Ethiopian chemist Tesfaye Lemma, working under the author's supervision at the Institute of Pathobiology in Addis Ababa.

Improved Extraction Procedures

Water extracts of powdered endod berries after defatting with benzene were more active in killing snails than were extracts obtained without a defat-

Figure 4.—Lemmatoxin-A



SOURCE: Parkhurst, et al. (32).

ting procedure. The concentration needed to obtain a 100 percent kill in 24 hours was 2 ppm. The increase in molluscicidal activity was proportional to the degree of defatting. The molluscicidal potency of a suspension of endod left to ferment over a period of time increased gradually for a long time (up to 5 months) if the endod concentrations were 10 to 20 percent. On the other hand, if the concentrations were 0.1 to 1.0 percent, the molluscicidal activity decreased within a few weeks. The best results were obtained when fermentation took place at 22° C (39).

The fermentation-based extraction procedure depends on practical, simple techniques using yeast cells that are part of the normal flora of the berries. When ground endod berries are soaked in water and left in a warm place, they ferment rapidly and eventually separate into a clear supernatant fluid containing the active principle, and a residue, mainly yeast cells and debris. The supernatant is easily separated from the residue and can be dehydrated with small, locally constructed solar drying chambers and ground into a fine powder. The powder then can be dusted directly over the infected water or prepared in different formulations such as flakes that can either sink or float on water depending on the specific snail targets; made into emulsion concentrates for spraying; or compressed into special briquettes of different hardness for slow release in water. In the case of briquettes, farmers and villagers could easily be taught how to prepare them, how much and how often (per week or per month) they should be applied, and at which specifically predetermined spots (based on the volume of water to be treated and the degree of hardness of the briquette) (5).

The simple fermentation chambers required and the drying and processing apparatus for this molluscicide could be constructed by students at neighborhood schools, a local blacksmith, or itinerant "barefoot technologists." The apparatus must be simple enough for easy operation by village-based community-health workers. Although preliminary studies to develop these possibilities have much promise, the packaging of technology and know-how have yet to be developed and standardized.

Yeast cells from the fermentation process can be washed, sundried, and used as high-protein supplements for animal feed, particularly as additives for chicken feed. These prospects, however, have not yet been fully studied.

Another useful tool to be developed is a simple procedure for colorimetric determination of the concentration of the active principle of endod in treated bodies of water. Such a device would allow more effective use of the product in the field (40).

Agronomic Studies

While research on the toxicity, chemistry, extraction, and application of endod has been progressing rapidly since the discovery of its molluscicidal properties in 1964, in general, studies on the agronomic aspects have lagged behind this research. Detailed investigations of the agronomic aspects of endod production were begun by Dr. Legesse W. Yohannes and his colleagues only in 1972. These efforts subsequently were enhanced by Dr. Charles B. Lugt, a Dutch agronomic chemist, sent to work in Ethiopia under a special grant from the Netherlands Government. A major goal of these studies is to select and breed plants for favorable growing characteristics, productivity, and high potency of berries. Endod is a dioecious plant but can be propagated readily from berries and cuttings. Some agrobotanical data on plant ecology, nutrition, germination, spacing, and irrigation have been gathered during the past few years, and studies on the ecology of the plant and its pests have been undertaken in Ethiopia (44).

The great climatic and ecological diversity of Ethiopia apparently has given rise to several geographic strains of *Phytolacca dodecandra* with varying growth characteristics, yields, insect resistance, and molluscicidal potencies. In a 5-year (1976-81) extensive agronomic study done on endod by Lugt, 65 different strains and varieties of the endod plant collected from different parts of Ethiopia were studied under comparable conditions. Three strains were selected for their exceptional growth characteristics, high molluscicidal potency (two to three times more potent than the originally used varieties), high annual yield (about 1,320 kg/ha), and high resistance to attacks by insect pests and drought conditions. The results of these studies have been published in a book by Lugt (41). The studies in Ethiopia also discovered that the green unripe endod berries contain more active molluscicidal components than the ripe pink berries, thus reducing time before harvest and damage done to ripe berries by birds (42,43).

One major difficulty with mass cultivation of endod is attack by larvae of a *Gitoma* drosophilid fly which bores through the stem, selectively killing young shoots of the plant (41,43). Although these insects can be controlled effectively by the application of appropriate insecticides, agronomic studies to select plant varieties with particular resistance to this insect have been promising.

In a current study, Dr. Hugh Bollinger of Plant Resources Institute, Salt Lake City, Utah, is undertaking endod tissue culture using the three selected strains of endod supplied from Ethiopia by Dr. Lugt. He is making significant advances on two fronts:

1. Development of tissue culture methods of mass propagation of selected vigorous strains of the plant through cloning. Plantlets developed through Dr. Bollinger's cloning method are being supplied to Ethiopia, Zambia, Brazil, and Swaziland for field evaluation. The new procedure should improve significantly the prospects for mass cultivation of known strains for large-scale field use.

2. Development of tissue culture system for in vitro biosynthesis of Lemmatoxin, the active principle responsible for killing snails. This exciting approach uses "*calus*" cultures with proven high molluscicidal potencies. Dr. Bollinger plans to expand these studies to produce the molluscicide and facilitate studies on nutritional and other biological characteristics of the plant.

Cost Effectiveness of Endod

Questions about the economy and cost effectiveness of endod should be investigated. During early stages of the study, it appeared that endod would be more costly than other molluscicides. However, two sets of questions must be asked before an adequate comparison of molluscicides to be employed in Third World countries can be made:

1. Does the molluscicide have to be imported from abroad? At what cost? For how long? Rapidly rising rates of inflation and the large quantities of molluscicide required on a continuous basis are key considerations. Can developing countries that are debilitated by schistosomiasis but have limited foreign exchange capabilities afford imported molluscicides?

2. Can the molluscicide be produced locally in sufficient quantities for large-scale use? If so, the initial cost of production during the experimental period presumably would be high, but what would be future large-scale production possibilities? At what cost? With what savings in hard currency and buildup of local agricultural and production facilities? The possibilities and cost of introducing modern agricultural techniques, better yielding plant varieties, and more insect resistant varieties should be included in this evaluation.

It seems that since local production and processing of a multiple use plant product for internal consumption and foreign sale is preferable to continued depletion of limited hard currency, the initial developmental costs should be considered as a high priority investment. As improved methods of cultivation and improved plants are introduced, costs should fall and both the usefulness and profit from the products should rise. As nonmolluscicide uses of endod, such as soaps, drugs, insecticides, and foaming agents, are developed, its cost effectiveness will increase proportionately.

The 1969-73 Adwa schistosomiasis control program that reduced disease transmission by about 85 percent used endod berries collected from wild plants or bought from local markets. The cost was Eth. $0.25 (US $0.10) per person per year (21).

Agrobotanical studies on endod in Ethiopia over the last 5 years under a special grant from the Netherlands Government have shown encouraging results. According to Dr. Lugt and his Ethiopian counterpart, Dr. Yohannes, selected strains of the endod plant can produce about 1,500 kg berries/ha/yr at the cost of about US $1,000 in local currency, while the German product, Bayluscide, costs about $25,000 per MT in foreign currency. Endod grown on only about 1 hectare of land would treat 1,200 ha of irrigated sugar cane, for which 91,000 MT of water per year are needed (41).

Where high-potency endod varieties (able to kill snails at 5 ppm) can be harvested directly from local farms, the ground or pressed berries could be applied directly to streams and irrigation canals, without need to concentrate or extract the molluscide. This would greatly reduce product and treatment costs.

Current Status of Research and Projected Activities

Field and laboratory studies on endod are being carried out in Ethiopia at the Institute of Pathobiology, Addis Ababa University. The Ethiopian Ministry of State Farms is collaborating with the Institute because of their interest in possible commercial farming of endod. The Ministry of Public Health is interested in the field applications of endod for schistosomiasis control in selected localities. However, owing to extremely limited financial resources available for such studies in Ethiopia, the level and intensity of research activities are very restricted.

During the period 1964 to 1974, molluscicidal and other properties of endod were intensively studied in Ethiopia, the Institute of Pathobiology in Addis Ababa, the Tropical Products Institute in London (8), the Stanford Research Institute in California (9), the Department of Epidemiology and International Health of the University of California in San Francisco (5), the Harvard School of Public Health in Boston (22), the U.S. Public Health Service laboratory and field stations in Puerto Rico, and the U.S. Naval Medical Research Unit (NAMRU-3) in Cairo, Egypt (5). Investigations conducted in other institutions in the United States, England, St. Lucia, Brazil, Egypt, the Sudan, Tanzania, and Japan on molluscicidal properties of endod under different conditions helped characterize its biological activity (5,46).

In addition to Dr. Bollinger's studies, Dr. John Lambert and colleagues at Carleton University and Ottawa University in Canada plan to undertake long-range toxicological and agronomic field studies on endod. The toxicological studies are intended to develop endod as a Canadian-backed and registered pesticide for possible widespread use as a molluscicide in different parts of the world. The ecological and agricultural studies, particularly of Dr. Lambert, involve the natural ecology of endod and determination of optimal conditions for growth and development of cloned plantlets, berries, and cuttings of selected strains for adaptation to different countries including Ethiopia, Zambia, and Swaziland. As a result of these recent developments, a renewed interest in endod is rapidly spreading among African and other countries. UNICEF has also shown interest in possible large-scale application of endod for schistosomiasis and other snail-borne disease control, especially with regard to its use on a community self-help basis, to be developed as part of UNICEF's integrated basic health services delivery programs in rural areas.

The Zambian National Council for Scientific Research held an "International Workshop on *Phytolacca dodecandra*" in March 1983, in Lusaka, Zambia, to bring these interested individuals and groups together, review work done on endod to date, identify shortcomings, delineate gaps to be filled, and develop specific areas and ideas for future work. A group of about 30 scientists with varying backgrounds from a number of African countries, the United States, England, and Brazil participated. The Lusaka meeting is expected to lead to further collaborative work on endod by participating experts as well as on other plant products and the control of schistosomiasis in general.

The benefits of endod go well beyond the potential applications of its many different properties, however promising they appear to be. It sets an example of local development of a natural product for multiple use that can be adapted to endemic social and cultural systems, raise the level of group participation and confidence, and improve the local and regional economy at minimal international cost and hard currency expenditure. Endod's major importance, however, is in the control of schistosomiasis and other trematode diseases.

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CHEMICALS FROM ARID/SEMIARID LAND PLANTS: WHOLE PLANT USE OF MILKWEEDS

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Abstract

The potential of arid/semiarid land plants as sources of commercial products is illustrated by the following examples: candelilla (wax); jojoba (oil, protein); *Acacia* spp. (gum); *Astragalus* spp. (tragacanth gum); guayule (rubber); rabbitbrush (rubber, chemicals); sunflowers (rubber, chemicals); yucca (soap); and cresote bush (antioxidants, phenolic resins). Co-evolutionary selection is a cause of the accumulation of secondary compounds in arid and semiarid plants. Although extraction of a single chemical might prove economically feasible for a few species, analyses involving extraction of multiple components and use of the extracted residue show that significantly greater value can be obtained by fractionation to attain whole-plant utilization. Although efficient laboratory methods to screen plants have been developed, only a few chemicals can be screened in the field. Additional research and development in field screening techniques are needed. Milkweed is a potential new chemical crop. The present stage of development is at the research, demonstration plot, pilot-plant phase. Milkweed is expected to be grown as a dryland crop in the western Great Plains using conventional farming machinery now used in alfalfa hay production. Large-scale plantation farming would have an impact on imports of fuel and other commodities. By providing an alternative cash crop for the western Great Plains, milkweed farming could greatly strengthen the agricultural economy of the region.

Introduction

To illustrate the utility of obtaining chemicals from arid/semiarid land plants, it is useful to examine some species that currently or potentially could produce industrial raw materials. Candelilla (fig. 1), *Euphorbia antisyphilitica* Zucc. (Euphorbiaceae), is the source of candelilla wax imported from Mexico (13). The market is good, but imports have dropped from 871 metric tons (MT) (960 tons) in 1978 to 379 MT in 1981 due to internal problems of procurement from native stands in Mexico. Candelilla wax sells for $4.19/kg ($1.90/lb) (16).

Figure 1

Candelilla, *Euphorbia antisyphilitica*, in a natural stand in the Chihuahuan Desert of West Texas and northern Mexico is a current source of high-valued wax

Jojoba oil is obtained from the seeds of *Simmondsia chinensis* (Link) Schneider (Buxaceae) in approximately 50 percent yield. This species is native to deserts of northern Mexico and Southwestern United States. The oil, composed of long chain esters that are stable under high temperatures, is useful as a lubricant (24). At present essentially all jojoba beans come from natural stands. The first commercial harvest of 3-year old plants in the United States is expected to be this year (1982).

Gum arabic is obtained from *Acacia senegal* (L.) Willd. (Fabaceae) which is native to arid lands of Africa and the Middle East (31). Acacia gum is used in adhesives, bakery products, candies, ice cream, cosmetics, and many foods to suspend solids and emulsify ingredients (31). The United States imports approximately 5,080 MT annually (17). The gum sells for approximately $1.57/kg (16). Over 100 *Acacia* species are known to exude gum. *Acacia berlanderi,* native to southern Texas and northern Mexico, appears to be a good candidate for a domestic gum source (31).

Another important gum (tragacanth) comes from *Astragalus gummifer* Labill. (Fabaceae) and related species. These *Astragalus* species grow in the high, cold deserts of Iran and the surrounding area. Gum tragacanth is used in pharmaceuticals, cosmetics, and as thickening agents in foods (31). Due to the political instability of the area, imports are erratic. Approximately only 126 MT were imported last year at a price of $83/kg (16). No other gum has been found that is a substitute for tragacanth gum. The species seem to be well adapted to the high, cold deserts of the Western United States.

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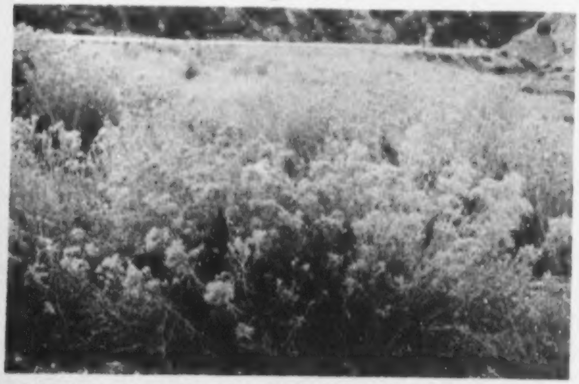
Natural rubber can be obtained from guayule (*Parthenium argentatum* A. gray (Asteraceae)), a desert shrub from the Chihuahuan desert of northern Mexico and west Texas (13). Its molecular weight is comparable to that of *Hevea brasiliensis* Mull. (44). The United States imports approximately 770,000 MT/year of natural *Hevea* rubber, principally from Southeast Asia (39). Guayule rubber production in Mexico reached a peak from 1941 to 1945 with approximately 36,400 MT being exported from Mexico (13). Natural rubber prices are about $0.95/kg (47). Two other sources of natural rubber are rubber rabbitbrush (*Chrysothamnus nauseosus* (Pall.)) Britton (21) (fig. 2) and sunflowers (*Helianthus* species) (40,41), all in the Asteraceae family.

Soaps for shampoos are being extracted from various species of *Yucca* (Liliaceae) (13). Biologically active compounds are obtained from many plants, the most familiar of which are morphine (opium) from *Papaver somniferum* L. and digitalis from *Digitalis purpurea* L. (46). *Larrea tridentata* (DC.) Coville (Zygophyllaceae), the creosote bush, is a potential source of nordihydroguaiaretic acid (NDGA) which may be used as an antioxidant (28) and in the production of phenolic resins (13).

Chemicals mentioned in the examples above generally are considered not involved in the primary metabolism of plants and are referred to as secondary compounds. It is now becoming apparent that secondary compounds may be of considerable importance to the survival of plants (37). Some secondary compounds repel deer (35), deter browsing by hares (8), and act as toxic and feeding deterrents in insects (42).

Herbivores can be divided into specialists and generalists. The specialist herbivores often prefer young leaves or rapidly growing tissue, whereas the generalists tend to prefer mature leaves and tissue (14). The generalists browse many different species, often over a considerable part of the year. Plants growing in arid lands can be subdivided into annuals, which take advantage of infrequent rains to grow to maturity and set seed quickly, and perennials, which have various adaptations enabling them to survive throughout the year. Major adaptations for drought survival are succulence (e.g., cactus), long roots to reach deep water tables (e.g., mesquite), and deciduous leaves during winter because many insects and animals may be inactive. Long-lived perennials need not reproduce every year, but they must survive drought, insects, diseases, and animal predation ultimately to reproduce. The evolution of environmental protection and more efficient metabolic processes is pitted against the relatively predictable selective forces of climate: natural variation in rainfall, wind, heat, and desiccation. In contrast, evolution of plant chemical defenses races constantly with the predator in a co-evolutionary battle.

Figure 2



Chrysothamnus nauseosus,rubber rabbitbrush, from Nevada, is a future source of industrial chemicals and natural rubber

After a plant evolves a new chemical or morphological defense, selection begins to operate on the predators that have mutations allowing them to overcome the plant defense. Perennial arid land plants tend to have morphological defenses (e.g., spines in cactus) and/or chemical defenses (e.g., bitter tasting phenolics in creosote). In more mesic regions, the species commonly can tolerate considerable browsing because adequate moisture is available for regrowth. As this is not the case in arid lands, it appears that accumulation of secondary products in arid land plants is necessary for survival. Since arid land plants have evolved and coevolved defenses for millions of years, these species are important for the discovery of fungicides, insecticides, and herbicides and as sources of accumulated secondary compounds.

Some major problems of growing plants in arid lands are that: biomass per area is low and harvesting costs may be expensive; wind and water soil erosion is already severe, so crops will have to be managed carefully; and a monoculture of an arid land crop, as with any crop, may allow the natural predators to increase.

Although initial emphasis may be on a single chemical or class of chemicals, few potential crops seem to be economically feasible if only a single product is obtained. Due to the costs of growing, harvesting, and extracting chemicals, each species should be examined for multiple uses (1,12). After the plant material has been collected at a central processing facility, the additional cost to process the material by several methods to extract additional products may not be large. For example, candelilla produces a fine wax, but this only accounts for 12 to 15 percent of the biomass. Cellulose from the remaining 85 to 88 percent can be used in fermentation or as an animal feed.

In general, nonpolar solvents extract chemicals that might be useful as waxes, lubricants, and elastomers. Polar solvents extract compounds that may be more useful as chemical intermediates, since they may contain highly reactive oxygen groups. They may be used as adhesives, coatings, UV absorbers, antioxidants, dyes, etc. The polar fraction has the greatest concentration of biologically active compounds (3).

The water or acidic aqueous fraction may yield a gum, such as tragacanth, or other valuable polysaccharides, such as pectin. Some water-soluble protein may be recovered at this step. The principal products left after extraction are cellulose, hemicellulose, lignin (if present), and protein. This residue can be nontoxic if biologically active compounds have been extracted previously. The residue may be used in several ways. Some of it may be burned to generate power at the processing plant. It may be burned in power generation stations in place of coal (12). Fiber may be removed during processing for use as paper, pulp, or fabric. The residue usually has an enriched concentration of protein and may be used as livestock feed. It could also be digested by fermentation to produce industrial chemicals (32).

Species with high yields of particular chemicals generally have been identified by solvent extraction in the laboratory (4,5,9,10,29). Field screening is extremely valuable once a selection program has begun. A rapid method to screen plants in the field would allow one to examine hundreds of plants per day and obtain seeds and cuttings immediately. Otherwise, each plant must be sampled and tagged. After the laboratory analysis, one must return to the field and find the desired individual. The plants may be from a remote site. The time lapse from the initial tagging through laboratory analysis to returning for germ plasm collection can span months or even a few years. In the meantime, the tags may be lost to wind or animals. Germ plasm could be collected at the time of initial sampling, but this necessitates collection and curing of a large volume of materials, 90 percent of which subsequently will be discarded. Collecting, preserving, and documenting field samples are time consuming activities and are major obstacles in massive screenings.

Two relatively new laboratory techniques have been developed for rapid screening: wide-line nuclear magnetic resonance (NMR) and near-infrared reflectance (NIR). Wide-line NMR is used in vegetable oil yield analysis because it specifically measures total hydrogen associated with only the liquids (oil and water) (36). Because NMR is nondestructive to oil seeds, plant breeders have used this technique extensively. Wide-line NMR is not portable enough for field screening and seems to be limited to liquid chemicals. NIR has a much broader potential range of applications. It has been used principally for seed oil and protein analyses (23,38). The plant material must be uniformly ground and its moisture content determined. NIR is, therefore, destructive of plant materials, although this is not a problem for whole plant chemicals. Field portable NIR units are available, but approximately 50 samples are needed for calibration on the large laboratory system to determine the optimum wave-length filters and regression equations. To my knowledge, Native Plants, Inc., is the only group that has tried to use NIR to predict the yield of a mixed group of chemicals—in particular, hexane and methanol extractables. Our results were not satisfactory. Further research is needed in this area.

Another method of field screening would be micropressure extraction coupled with a portable microwave oven and sensitive electronic field balance. Although this method probably is feasible, to my knowledge no one has developed such a system.

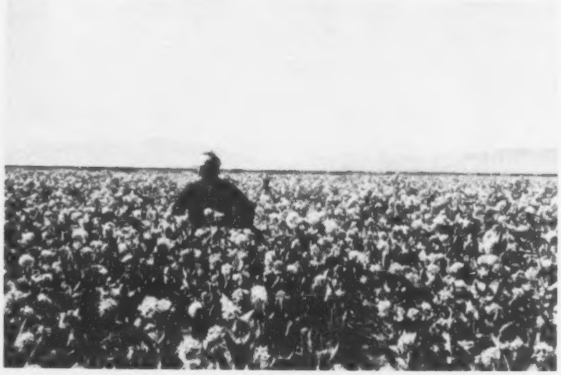
One major difficulty in developing a field screening technique is that chemicals of interest may not have unique spectral qualities or any reactive groups to which specific stains can be applied for color tests. The polar chemicals are more likely to have strong spectral properties and unique color reactions with reagents. For example, a color test for alkaloids is quite specific and relatively easy to do. However, a specific color test for only one alkaloid in a family may not be possible.

In summary, adequate field screening techniques for chemicals are not available. This is a serious obstacle to future development of chemical crops.

Milkweed

As part of a long-term study to discover new crops for production of phytochemicals, Native Plants, Inc., has been studying the showy milkweed (*Asclepias speciosa* Torr.) (fig. 3). The genus *Asclepias* includes approximately 140 species (48,49). All cytologically known species are diploids. Interspecific hybridization is reported to be extremely rare in spite of widespread self-sterility

Figure 3



A test plantation (5 ha) of showy milkweed, *Asclepias speciosa*, near Syracuse, Utah

(49). The North American species generally are erect, herbaceous perennials, although a few annuals are known (48).

No rhizomatous North American species are known except *A. syriaca* which "may produce gemmiferous roots giving rise to clones of limited extent" (48). However, rhizomatous growth has been observed in *A. latofolia* (R. Adams, observation). *Asclepias tuberosa* is reported to live over a century (48).

Due to the wide distribution of *A. speciosa* and its apparent ecological success, this taxon was selected for intensive research on its domestication potential as a source of phytochemical products. *Asclepias speciosa*, the showy milkweed, is widely distributed from near the Mississippi River westward to the Pacific coast and from central Saskatchewan and Alberta south to central Oklahoma. West of the Rocky Mountains, it is chiefly found along banks of irrigation ditches. It produces a feathery plume on the seeds which are easily dispersed. In Minnesota, the northeastern part of its range, it competes with crops and can cause significant problems.

Milkweed Products

Hexane extracts of the aerial parts of *A. speciosa*, obtained by Soxhlet extraction for 20 hours, are dark green. The pigments are removed by decoloring (11), and natural rubber (*cis*-1,4-polyisoprene) can be removed by acetone precipitation followed by centrifugation. The decolorized, rubber-free hexane extracts have been subjected to analysis by thin layer chromatography (TLC) and glass capillary gas chromatography (GC) and gas chromatography mass spectroscopy (GC/MS) (in Tri-Sil 'Z'; Pierce Chemical Co.). Over 90 percent of the constituents of the hexane extracts could be identified and quantitated in this manner (2,3).

Pigments, mainly chlorophylls, account for approximately 11 percent of the hexane extract, and low molecular weight rubber accounts for approximately 2 percent of the extract (table 1). The nonpolar extracts contain small amounts of fatty acids, alcohols, hydrocarbons (alkales and squalene), monoglycerides, and phytosterols. Cardenolides were not detected in the hexane extract by TLC using the Kedde reagent for visilization (2). Approximately 85 percent of the nonpolar extract consists of derivatives of α- and β-amyrin related triterpenes (2). Over 60 percent of the decolorized, rubber-free hexane extract consists of α- and β-amyrin acetates, present in a ratio of about 5:1. Smaller amounts of the corresponding butyate, caproate (hexanoate), and palmitate esters of these triterpenes were found in roughly the same ratio of α- to β-derivates.

The methanol extract of the aerial parts of *A. speciosa* following hexane extraction consists chiefly of inositol and sucrose (table 1). Other minor constituents identified by GC/MS in the methanol extract include malic acid, pyroglutamic acid, methyl pyroglutamate, citric acid, proline, methyl ferulate, and trace quantities of numerous carbohydrates. True phenolics account for only a minor part of the methanol extract, so *A. speciosa* does not seem to be a promising source for the economic extraction of "polyphenols" (table 1). Low polyphenol content has previously been reported for A. syriaca (20).

Also present in the methanol extract of *A. speciosa* are small quantities of cardenolides (demonstrated TLC using the Kedde reagent). Plants in the genus *Asclepias* biosynthesize varying amounts of toxic cardenolides (7). Aside from their digitalis-like toxic effects on the heart, cardenolides from *Asclepias* species affect the lungs, kidneys, gastrointestinal tract, and brain of experimental animals (6,7,22,34). They also possess general cytotoxic activity (26,27).

An additional acidic aqueous extraction of milkweed yielded approximately 4 percent pectin, a cell wall constituent present in all higher plants (3). Pectin is a valuable product ($3.91/kg) (16) but is difficult to extract and purify.

The milkweed residue, after *exhaustive* extraction with hexane and methanol, seems to be nontoxic and equivalent to alfalfa hay in digestibility by sheep (18). In research carried out by Native Plants, Inc., *Asclepias speciosa* was harvested in full flower (June 26, 1981) and extracted with hex-

Table 1.—Proximate Analyses and Product Values of Milkweed

Product	% Yield	Value $/kg ($/lb)	Product value from 1 MT (t)
Hexane extract	3.8		
Pigments	0.4	0.22(0.10)*	0.88(0.80)*
Natural rubber	0.1	0.95(0.43)+	0.95(0.86)+
Tri-terpenoids, esters and related compounds	3.3	0.24(0.11)*	7.92(7.19)*
		3.30(1.50)+	108.90(98.82)+
Methanol extract	17.5		
Sucrose	6.0	0.68(0.31)	40.92(37.13)
Inositol	0.9	24.00(10.90)	216.00(196.00)
Polyphenolics	1.1	0.13(0.06)*	1.43(1.30)*
		0.55(0.25)+	6.05(5.60)+
Residue			
Pectin	4.0	3.91(1.78)	156.40(141.92)
Fibers	5.0	0.47(0.21)	23.50(21.32)
Livestock feed	70.0	0.09(0.04)x	63.00(57.17)x
		0.13(0.06)y	91.00(82.58)y
Total gross value per MT (t)		Low	511.00(463.70)
		High	644.60(584.94)

*Price based on Btu content.

+Price based on substitution for an appropriate chemical feedstock

xPrice based on low hay value.

yPrice based on high hay value.

SOURCE: Adams, et al., 1983; Adams, Balandrin, and Martineau, 1983. Prices: *Chem. Mkt. Rptr.*, Nov. 8, 1982, and *Wall Street Journal*, Nov. 1, 1982.

ane/methanol. The residue contained 16.3 percent crude protein (N × 6.25), which is similar to alfalfa hay (16 percent) and greater than corn grain (9.7 to 10 percent) (1). Amino acid analysis of the sample revealed that the amino acid content is comparable to alfalfa and generally superior to corn grain (1). The protein has high amounts of lysine (280 percent of the corn value) and a greater concentration of the essential amino acids than corn (1).

All toxic constituents in showy milkweed could be removed by exhaustive methanol extraction. The feasibility of using showy milkweed as an animal feed, therefore, depends on detoxification of the residue, either by high extraction efficiencies, heat, or acid treatment. The detoxification of the residue must be established by feeding trials.

The total gross value of products that could be obtained from nonselected (wild) *A. speciosa* ranges from $511/MT to $645/MT. Unfortunately, several technological problems need to be solved before its commercial potential can be realized. Commercially viable extraction and purification of the two highest value products, inositol and pectin, have not been demonstrated. Both products are expensive because they are difficult to extract and purify. In addition, inositol and pectin have limited markets: inositol, 0.45-0.9 million kg (R.W. Greef & Co., pers. comm.); pectin, 1.6-1.8 million kg (15). If the technology is developed, demand for these products could support a small 6,000-ha plantation, but could not sustain unlimited sized plantations as would be the case for some petrochemicals.

All current extraction processes for milkweed use hexane followed by methanol in a conventional extractor, such as the Crown extractor. To date, two proto-commercial extractions have been made, one at the POS (Protein-Oil-Starch) pilot plant at the University of Saskatchewan and the other at the Northern Regional Research Center, ARS, USDA, in Peoria, Ill. Extraction efficiencies at the POS Pilot Plant were only 67.5 percent for the hexane-soluble material and 55.7 percent for the methanol-soluble material (18). Problems were encountered with fine particles plugging the system and in pumping the viscous hexane extract after partial solvent removal. Additional research is needed on grinding, particle sizing, extract handling, and extraction residence times. Research also is needed on decolorizing the hexane extract and separating rubber from triterpenoids. As previously mentioned, considerable technological development is needed before the production of inositol and pectin is commerically feasible. More efficient methods are needed for detoxification of the livestock feed.

Agronomics

Plant Establishment

The optimum planting methods for milkweed are not well known. Native Plants, Inc., has successfully established a 4-ha plot in Utah and small test plots in New Mexico, Texas, and Kansas. We have experienced establishment failures in Texas, Utah, and Saskatchewan, Canada. Additional research is needed on depth and time of planting. Density trials have indicated that a closed canopy yields higher biomass.

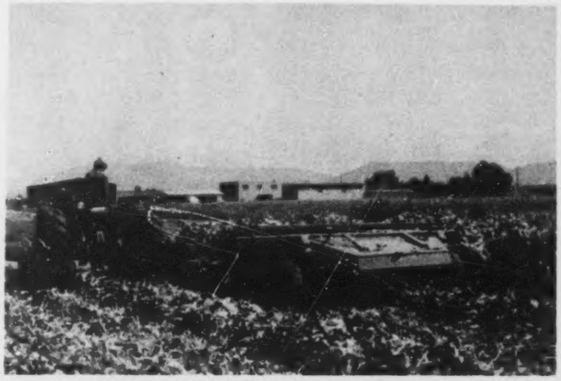
Weed Control

Weed control is a major problem with milkweed, especially during stand establishment. During the seedling stage, milkweed seems to direct most of its energy into root development. This contributes to drought tolerance, but the above-ground portion grows slowly and is not competitive with fast growing weeds during the first year after establishment. A selective, pre-emergent herbicide must be developed for use during the first year. In the absence of such an herbicide, Roundup® was used prior to emergence to control hard-to-kill perennials such as salt grass (*Distichlis stricta*) and common mallow (*Malva neglecta*). A wick applicator has been used to apply Roundup® to control the taller weeds during the season. Weed control is perhaps the most critical research need for the economical production of milkweed.

Harvesting and Yields

All of the equipment used in growing milkweed is standard farm equipment readily available to

Figure 4



Harvesting of milkweeds uses conventional farm equipment for cutting, crimping, and baling western farmers. Harvesting has been performed with equipment used in alfalfa haying operations. Harvesting techniques are essentially the same for milkweeds as for alfalfa hay.

A. speciosa test fields, 2 ha (5 ac) planted in rows 91 cm (36 in) apart, were first harvested on June 26, 1981. The plants were cut and crimped with a hay conditioner and swathed into windrows. Stems were dehydrated to a dry crack stage and baled within 3 days. The leaves dried considerably faster and became brittle. Some losses due to leaf shatter occurred during baling. Hay that fell into the furrows between rows could not be picked up by the baling machine, resulting in additional crop loss.

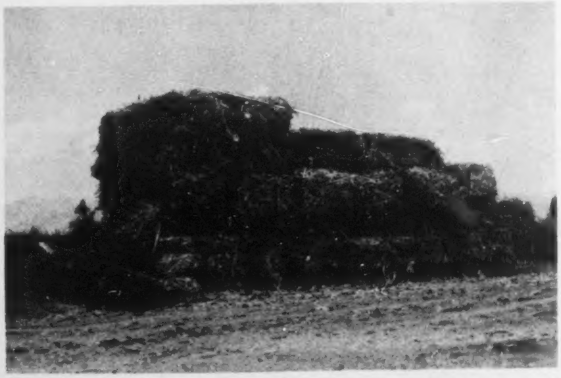
In 1982, our two fields of 2 ha each averaged 4.35 MT/ha and 4.26 MT/ha, respectively. Annual precipitation in the area is approximately 50.4 cm. Denser stands are expected to yield between 6.7 MT/ha and 9.0 MT/ha.

Crop Storage

There would be a considerable economic savings in plant capacity if an energy/chemical crop could be stored and processed throughout the year. Two apparent methods for storage are fresh-cut as silage (70+ percent water) and dried as hay (15 to 20 percent water, fig, 5). Because both procedures use existing farm equipment, they would not require extensive new equipment or costly acquisitions by farmers.

Native Plants, Inc., carried out some tests on the effects of storing milkweed. Five bales were stored uncovered under ambient conditions. This storage test presented the worst possible conditions. The bales were subjected to several feet of snow in the fall and winter and a number of freezing and thawing cycles. The nonpolar extractables were found to be quite stable over time. For example, the nonpolar extracts of the March sample after 8 months of storage (3.75 percent ± 2 (0.116)) were not significantly different from the first month's sample taken in August (4.07 percent ± (0.072)). The methanol extractables, however, showed a sharp decline after 2 months of storage and a gradual decline thereafter. This decline probably is due to the catabolism of carbohydrates by microorganisms during the rotting.

Figure 5



Milkweed is stored in conventional bales until processed for the removal of chemicals

Three additional storage conditions have been studied: bales stacked in a barn; bales stacked in the open and covered with clear plastic; and bales stacked in the open and covered with black plastic. The nonpolar extractable yields show no significant differences. The methanol extractables yields decreased only slightly.

In general, it seems that moisture and subsequent rotting are the major potential problems associated with storage of baled milkweeds. This generally is not a problem in semiarid lands. In moister areas, the bales could be covered with either clear or black plastic.

Agricultural Scale

A survey of vegetable oil processing facilities revealed that processing plants range in capacity from 91 MT/day to 1,090 MT/day. An extraction plant with a capacity of 91 MT/day would process 27,300 MT/year, given the current yields from *wild* milkweed (4.3 MT/ha) and assuming a processing season of 300 days/year. This would require a 6,349-ha plantation. If 100 percent of this area were planted, it would represent a block approximately 8 km x 8 km. If only 25 percent of the area were planted to milkweed, the plantation would be equivalent to a 16 km x 16 km block, with a maximum haul distance to a centrally located plant of 11.31 km. This compares favorably to current maximum haul distances on the western Great Plains for grain and ensilage (24 to 32 km.).

Milkweed (*A. speciosa*) is distributed widely over a range of climate and soils. It appears that milkweed can be grown easily in the western Great Plains of the United States. This area is mining water from the Ogallala aquifer, and water shortages are resulting in a steady reversion from irrigated to dryland farming (43). The introduction of a new dryland crop will compete for land with dryland wheat, grain, sorghum, and sunflowers. However, this land is not very productive and the dryland crops contribute only a small portion to total

U.S. production of these crops. The cost of farming milkweeds eventually may be comparable to farming dryland alfalfa. The first year of growing milkweeds has been difficult due to the lack of an effective method of weed control and problems in stand establishment and obtaining a uniform stand. In order to displace dryland wheat or grain sorghum, the new crop must be more profitable for the farmer. An examination of yields and prices (45) of Hansford County, one of the most productive counties in the northern plains of Texas, shows the precarious position of present farming units. The average dryland yield of wheat for Hansford County for 1976 through 1980 was only 30.4 bu/ha (824.5 kg/ha) and the gross income was only $104.89/ha (table 2). The economics of grain sorghum is similar; the average yield was 1,508.8 kg/ha, which returned an average of $135.44/ha. If one could introduce a new crop that costs approximately the same as dryland wheat or grain sorghum to grow, the gross revenue needed to displace one of these crops probably would be about 20 percent greater than the present gross income of $135, or $162/ha.

Table 3 shows the variable production costs in 1982 for a 2-ha field in Syracuse, Utah. Based on 4.5 MT/ha using "wild" milkweed seed, the production costs were $418.45/ha or $92.99/MT. Of the $418.45, $233.13 was spent on weed control. More economical weed control is a priority for reducing milkweed farming costs. The other large expenditure was harvesting. Because relatively small farm equipment and small bales (30 kg) were used, conversion to larger swathing equipment and to stack loader bales or round bales (450 kg) could represent a considerable cost reduction. In any case, dryland milkweed cannot be grown as cheaply as dryland wheat or grain sorghum. On the other hand, the products obtained from milkweed promise to be of much greater value than those from wheat or grain sorghum after efficient processing technology is developed. One should also note that the cost drops from $92.99/MT to $53.85/MT if yields can be increased from 4.5 to 9.0 MT/ha (table 3). Research in breeding, selection, and agronomic development, resulting in increased yields, will have a positive impact on the profitability of milkweed.

Impacts

The development of a new crop which does not compete directly for a market share with the traditional food/fiber crops (e.g., wheat, corn, grain sorghum, soybeans, sunflowers, cotton, etc.) could free the U.S. farmer from his dependence on pro-

Table 2.—Yields and Gross Income From Dryland Wheat and Grain Sorghum in Hansford County, Tex., for 1976-80

	Wheat			Grain Sorghum		
Year	Yield bu/ha	Price/ bu	Gross Income/ ha	Yield lb/ha	Price/ lb	Gross Income ha
1976	21.0	3.17	$ 66.57	3326.0	.0355	$118.07
1977	19.8	2.14	42.37	3019.6	.0315	95.12
1978	3.9	2.92	8.76	2236.3	.0392	87.66
1979	61.0	3.82	233.02	5779.7	.0438	253.15
1980	46.7	3.72	173.72	2273.3	.0542	123.21
Avg. Yield	30.3 (= 824.5 kg/ha)			3327.0 (= 1508.8 kg/ha)		
Avg. Gross Income/ha			$104.89			$135.44

SOURCE: Texas Department of Agriculture, 1981.

Table 3.—Variable Production Costs for Milkweed in the Second Year of Production at Syracuse, Utah, 1982, 1 Harvest (4.5 MT/ha, or 2 t/ac) and Prorated Costs @ 9 MT/ha (4 t/ac)

Variable Cost	Basis: Rates and Materials	Costs @ 4.5 MT/ha	Prorated Costs @ 9 MT/ha
Herbicide	2.5 gal/ha Roundup @ $72.00/gal.	180.00	180.00
Spray	Machine and labor, $6.18/ha	6.18	6.18
Swath	Machine and labor, $22.41/ha	22.41	22.41
Bale	$12.10/MT, 4.5 MT/ha	54.45	108.90
Pickup and Haul Bales	$.23/bale x 150/ha	34.50	69.00
Fertilizer	80.4 kg/ha (160.8 kg/ha) 34-0-0 @ 0.28/kg	22.51	45.02
Spread Fertilizer	Machine and labor, $6.18/ha	6.18	6.18
Herbicide	0.93 gal/ha Paraquat @ $44/gal	40.77	40.77
Spray	Machine and labor, $6.18/ha	6.18	6.18
Total Variable Costs/ha		418.45	484.64
Cost/MT		92.99	53.85

SOURCE: DOE Final Report, 1982.

ducing surplus commodities. The major milkweed products would have an impact on the following markets:

- triterpenoid: could substitute for oil imports if converted to fuel or used for a lubricant, or for foreign wax imports if converted to fuel or used as a wax.
- sucrose: could substitute for foreign, and possibly some domestic, sugar markets, although only a small impact would be anticipated in this high-volume market.
- inositol: could substitute completely for imported inositol; all inositol currently is imported, mostly from Japan, with lesser amounts from China.
- pectin: could substitute completely for domestic and imported pectin, apparently now all produced from citrus peels.
- fiber: could compete with Douglas fir, tamarisk, and other woods for the paper-pulp market; impact probably would be insignificant.
- livestock feed: could compete with corn ensi-

lage, alfalfa, hay, possibly small grains. Impact could be considerable, particularly since the western Great Plains is a center of cattle feeding operations. The local cattle feed (grain corn, corn ensilage, grain sorghum) has been produced with water from the Ogallala aquifer which is being depleted (43). A replacement source of cattle feed will be important for survival of western Great Plains feedlots.

Development of milkweed as a crop will have a positive economic impact on agriculture of the western Great Plains. With essentially stable grain prices and increasing operating costs, the farming economy of that region is severely depressed and many farmsteads may fail soon.

The current strategy for the establishment of a commercial milkweed plantation is to encourage a large company with sufficient financial resources to contract the required amount of land (6,400 ha) to be planted and harvested. The company would begin construction of the processing plant with the appropriate lead time. Each farmer probably would be offered a guaranteed profit or gross price per hectare, depending on the company's confidence in the projected growing costs and yields of milkweed. The first year's contract would be a total expense for the company and would have to be prorated over several years' income. After a few years, the company would probably begin to pay the farmer on a per-ton basis to encourage farming efficiency. Since it is likely that milkweed will produce several products, the market's risk would be buffered. Ultimately, if products are obtained that feed into fossil fuel related markets, it is conceivable that many millions of hectares will be farmed with milkweed or similar crops. This would have some impact on U.S. wheat and grain sorghum production, but considerable idle land is available for growing these traditional crops if the price increases sufficiently. Since 80 to 90 percent of our grain production is used for livestock feed, the loss of the dryland wheat and grain production in this area would have to be compensated by production of livestock feed as a byproduct of the operation. For example, suppose a farmer who produces an average of 1.35 MT/ha of wheat begins to grow 4.5 MT/ha of milkweed. The wheat has approximately 11 to 14 percent protein. After extraction, the yield of milkweed residue would be 3.15 MT/ha (70 percent of 4.5 MT/ha) (table 1) of 12 to 16 percent protein livestock feed. Even if the extractable yield were increased to 50 percent, the residue would equal 2.25 MT/ha of 12 to 16 percent protein livestock feed. Thus, the battle between food and fuel (or chemicals) can be muted effectively if crops are developed that contribute significantly to livestock feed. Only a small portion of grain produced is used for human consumption, so the vast grain producing area from central Kansas eastward through Iowa, Illinois, Indiana, and Ohio still could produce all our necessary food grain.

Constraints

The principal constraints to developing such a system are scientific and economic factors. Selection and breeding are needed. Extraction and processing technology must be developed. There is a need to continue research on product development and industrial use. Establishing a plantation and extraction facility will be expensive. Native Plants, Inc., is working with a major oil company that has the resources to initiate such a venture. Few corporations will have both the resources **and** the desire to enter into this technology.

Many environmental constraints were considered when selecting milkweed as a potential crop. These include drought, wind, heat, cold tolerance, and soil constraints. A major concern in the western Great Plains is soil erosion, particularly by wind. This could be a severe constraint unless adequate stubble is left in the field to prevent wind and water erosion. Strip harvesting could assist with erosion control. Leaving stubble in the field would also help compensate for the loss of soil humus by continued cropping. The problem of a general decline in critical soil minerals may be alleviated partially by recycling manure from the cattle feedlots.

Sustainability of the Resource Base

The rapid loss of irrigation water from the Ogallala aquifer in the western Great Plains (43) signals a potential change in the agricultural output of this region. The proposed new crop will be grown dryland in that region, so will not have a significant impact on ground water resources. Growing milkweed may affect the local farmer. For example, because bees obtain nectar from milkweed flowers, the potential exists for development of a honey bee industry. Monarch butterfly larvae feed on milkweed. It is anticipated that these populations will increase. Aphids are a serious pest on milkweed and probably will be controlled by both natural predators and insecticides. As already mentioned, soil fertility will decline, approximately in proportion to the amount of biomass removed. Nitrogen is one of the principal elements that will have to be replaced.

In general, our goal is to promote an ecologically sound approach to land and crop management. Growing milkweed and other plants that are adapted to arid and semiarid conditions offers an unusual opportunity to apply a biorational approach to new crop development on lands with a limited water supply. The constant process of coevolution of plants with other plants, insects, and animals provides a great untapped source of phytochemicals for industrial chemical feedstocks.

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INSECTICIDES, INSECT REPELLANTS, AND ATTRACTANTS FROM ARID/SEMIARID-LAND PLANTS

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Abstract

Four weeds (*Acorus calamus, Artemisia tridentata, Heliopsis longipes,* and *Tagetes minuta*) and three cultivated plants (*Azadirachta indica, Mammea americana,* and *Ocimum basilicum*) are potential candidates for crop development and commercialization for sources of insect attractants, repellants, or toxicants. Although all could be commercially viable, the neem tree (*A. indica*) is by far the most likely to succeed. Its development in the Southern United States and Central and South America is highly recommended.

Introduction

The plant kingdom is a vast storehouse of chemical substances manufactured and used by plants as defenses against insects, bacteria, fungi, and viruses. The American Indians and native tribes in Central and South America, Asia, and Africa have used and, in some places, still use decoctions from many plants as medicines for a wide variety of ailments (30). The efficacy of these materials for relieving pain and suffering is described by Ayensu (5) in the introduction to his "Plants for Medicinal Uses With Special Reference to Arid Zones."

Dioscorides (A.D. 40-90) divided poisons into three classes: animal, plant, and mineral. He listed opium, black and white *Hyoscyamus, Mandragora, Conium,* elaterin, aconite, and the juices of *Euphorbia* species as plant poisons. He was also aware of colchicum's medicinal properties. The Romans used *Veratrum album* and *V. nigrum* as medicines, constituents of "rat and mice powders," and insecticides. From the time of the early Romans to the 20th century, only three efficient insecticides were discovered: nicotine, pyrethrum, and hellebore. The discovery of rotenone and several other plant-derived insecticides followed in rapid succession. Today, a wide variety of plants has been shown to be effective not only as insect toxicants but also as repellents, feeding deterrents, attractants, inhibitors of growth and development, and sterilants. Useful general references on the subject of plant-derived physiologically active materials for insects are those by Jacobson and Crosby (24), Feeny (11), Kubo and Nakanishi (31), Finch (12), Jacobson (20,22), and Smith and Secoy (50).

Although arid/semiarid land plants do not produce compounds that are more biologically active against insects than other plants, they lend themselves more readily to mass cultivation than plants requiring fertile soil for growth and development.

Since promising pesticidal plants are too numerous to mention here, only the seven with the most commercial potential are discussed. The scientific name, common name (if known), and family of each plant are given, followed by a discussion under the following headings: description, native range, present and potential uses, active compounds, extraction, cultivation, and constraints to development.

Discussion

Acorus calamus L.

Common names: Calamus, sweetflag

Family: Araceae

Description: A. calamus is a semiaquatic, robust perennial that can grow on dry land, is 1.5 to 1.8 m (5 to 6 ft) tall, has a horizontal rootstock containing aromatic cells and iris-like leaves, and grows at an altitude of 900 to 1,800 m (3,000 to 6,000 ft). It is winter-hardy and flowers in early summer.

Native range: The American variety grows wild in various provinces from Florida to Texas, Idaho, Ontario, and Nova Scotia. The Indian variety is indigenous to the plains of India and Burma, Ceylon, and the Celebes Islands. The Japanese variety occurs throughout the country. The European variety occurs throughout the continent.

Present and potential uses: The roots have been used from ancient times in India and Japan for the treatment of a variety of ailments and as an insect repellent and toxicant. The essential oils from the roots of the Indian and European varieties are obtained by steam distillation or solvent extraction of the crushed rhizomes. These oils, reported to be repellent and toxic to clothes moths, house flies, fleas, several species of mosquitoes, lice, and several species of stored grain insects, are available commercially. When the finely powdered rhizome is mixed with various grains in a ratio of 1:50 (0.9 kg to 45.5 kg) the grains are free from insect damage for a year. The dried rhizomes and leaves, as well as their water infusions, are effective against crop pests such as plant lice and beetle grubs (18,19). The

Indian root oil, which is obtained in 5 to 10 percent yield, is much more active than that obtained from the Japanese variety which is obtained in less than 1 percent yield. The oil causes sterility in male house flies, and low concentrations hamper the maturation of ova and cause complete regression of the ovaries. The Indian oil, and to a lesser extent the European oil, is highly attractive to female Mediterranean fruit flies, female melon flies, and male and female oriental fruit flies (25). The roots are used as an insecticide and vermifuge in China.

Active compounds: The major distilled oil component (80 percent) responsible for the repellency and sterility is β-asarone, or (Z)-2,4,5-trimethoxypropenylbenzene. Another component, asarylaldehyde (2,4,5-trimethoxybenzaldehyde), also is repellent to many species of insects. Both compounds are attractive to fruit flies (25). Synthesizing β-asarone and related compounds by a process that gives an overall yield of 79 percent is cheaper than extracting the oil from calamus. The compounds are expected to be especially useful as fumigants for protecting stored grain from insects, as they will permeate grain-filled storage areas without leaving residues on the grain after the areas are ventilated. The rice weevil, probably the most damaging insect pest of stored grains, is vulnerable to β-asarone (2). Asarylaldehyde is available commercially.

Several other compounds obtainable from calamus oil are acoragermacrone, which is attractive to female melon flies but is not available synthetically (25); at least eight coumarins which are potentially useful in the treatment of tuberculosis (38); and a host of terpenes which have superior germicidal properties (49) and are used in perfumery (13).

Extraction: Raquibuddowla and Haq (43) have published the details of a countercurrent pilot plant method for extracting the oil from the rhizomes with petroleum ether, which can be recovered and reused. Three extractions of 25 kg of ground rhizomes (1.65 mm particle size) at room temperature yield 2.71 kg of oil, from which the active compounds can be isolated by fractional distillation or column liquid chromatography (25).

Cultivation: The plant is propagated by division. It propagates easily in the spring or autumn and although it thrives in moist soil, it may be grown on dry land.

Constraints: β-asarone has a marked depressant effect on the central nervous system of mice, rats, and monkeys. It reduces spontaneous locomotor activity in mice and rats, and in monkeys produces a calming effect lasting 24 hours. The onset of action is more rapid than that of reserpine (9). Although these pharmacological properties may limit the use of calamus oil to certain applications, they should not prevent use of the oil for agricultural insect control and possibly for medical purposes.

***Artemisia tridentata* Nutt.**

Common name: Big sagebrush

Family: Asteraceae

Description: A. tridentata is a copiously branched perennial which has short rhizomes, is aromatic, and grows to a height of 3 m. The inflorescence is generally dense and leafy; the flowers are fertile and bloom from July to September. The three-toothed leaves are 2.5 cm long. The plant thrives in light, well-drained, dry, stony soils.

Native range: Originally a native of Europe, it is the prevailing plant of the Great American Desert, which centers around the Salt Lake of Utah and includes portions of Utah, Colorado, northern Nevada, and northern Arizona. It is also found in the desert areas of Washington State, in British Columbia, and in Baja, Calif.

Present and potential uses: Cattle browse this plant on the range. The Indians sometimes use the brittle branches for thatch. The seeds are eaten by many kinds of birds and mammals, and California Indians grind the seeds into a meal used for making a kind of pinole. An extract of the pollen is used to treat hay fever.

An ethanol extract of the dry branch ends is exceptionally effective in preventing feeding on potato leaves by the Colorado potato beetle, *Leptinotarsa decemlineata* Say (28). The beetle's resistance to insecticides in potato-growing areas is an increasingly serious problem in several areas of the world, and this resistance probably will become more widespread. Antifeedants could be important in a multiple system approach (integrated pest management) to control this pest (27). In classical times, the leaves and shoots of *Artemisia* species were added to stored cereals in granaries to protect them from weevils and other pests, and the water in which they had been steeped was used to kill or repel insect larvae, fleas, and locusts. Several species of ticks are killed rapidly by exposure to the vapors of the powdered plant (19). Various parts of the plant are used in the United States as a vermifuge.

Active compounds: Although one of the feeding deterrent compounds in the branches has been identified as deacetoxymatricarin, other compounds not yet identified are also responsible for the activity. Deacetoxymatricarin shows good antifeedant activity at a threshold of 20 micrograms/square centimeter ($\mu g/cm^2$). An extensive series of sesquiterpene lactones and a number of coumarins including esculetin, scopoletin, 7-hydroxycoumarin, and 6,7-dimethoxycoumarin are present in the plant. Strangely, although a steam distillate of *A. tridentata* at 80 $\mu g/cm^2$ had no effect on the feeding activity of *L. decemliniata*, an aqueous extract of the organic residue following steam distillation showed strong activity at 5 to 10 $\mu g/cm^2$ (28). Numerous species of *Artemisia* contain absinthin, which is avoided by insects (15).

Extraction: The dried, ground branches are extracted with ethanol, then the extract is freed of solvent and partitioned between 70 to 90 percent aqueous methanol, chloroform, and carbon tetrachloride. Most of the deterrent activity is from the carbon tetrachloride portion, which is chromatographed on a silicic acid column eluting with successively more polar solvents (28).

Cultivation: Sagebrush has been cultivated since 1881. It can be planted at any time during October and March in full sunlight, and grows rapidly.

Constraints: Seed germination is low—35 percent or less. The pollen is known to cause hay fever. Deacetoxymatricarin has not been synthesized and it is unlikely that it can be synthesized economically for high yields because a number of inactive geometrical isomers might be formed instead. There should be no practical problems in using crude plant extracts for crop protection, as these can be sprayed on crops without purification (52). A more extensive search for insect antifeedants in sagebrush desert plants certainly is justified.

Azadirachta Indica A. Juss.

Common names: Neem, nim, margosa

Family: Meliaceae

Description: The tree is of moderate to large size (12 to 19 m tall) with a straight trunk that can attain a diameter of 1.8 m. The bark is moderately thick; the heartwood is red, hard, and durable; and leaves are glabrous and resemble those of marijuana. Neem bears honey-scented white flowers.

Native range: Neem commonly occurs in large numbers in the open scrub forest in the dry zones of India and Burma. It was introduced as an ornamental into East Africa in the last century. It is also well established in Guinea and the Sudan (39).

Present and potential uses: Almost every part of the neem tree is used medicinally in India. The timber is durable, is seldom attacked by termites, and can be used for the manufacture of building materials, furniture, and other wooden objects of commercial value. In India, goatskins treated with tannins derived from the bark compare favorably with hides processed by conventional chemicals. The amber-colored gum exuded by the bark is used medicinally as a stimulant (53). The twigs have been used for many years in India and Africa for general mouth hygiene, and extracts of the bark are used in toothpaste in Germany. Neem leaves are useful fodder for farm animals and are reputed to have therapeutic effects against intestinal worms and ulcers (37).

The seed has the most commercial promise. For centuries seed oil has been used in India for the manufacture of a refreshing soap and has been burned as a source of light and heat. The oil can also be used for the manufacture of wax and lubricants. The seed cake left after oil extraction is used as an organic manure for fertilizing cash crops of sugarcane and vegetable gardens in India (40,41, 42). Although all parts of the tree repel insects, extracts of the seeds are outstanding repellents and feeding deterrents for a broad spectrum of economic agricultural and household insects. Seed extracts deter at least 25 species of crop pests in the United States from feeding, inhibit the growth and development of others, and render others sterile (10,21,42, 48,56).

Unlike most of the present insecticides available on the market, the seed extracts appear to be nontoxic to man and animals and are essentially nonphytotoxic. In addition, they have a systemic action when applied to some crops so that, once absorbed by the plant tissue, they offer more durable protection to crops even after heavy rain showers.

Active compounds: Of the three proven insect feeding inhibitors isolated from neem (meliantriol, azadirachtin, and salannin), azadirachtin is by far the most effective, since it can be used at concentrations as low as 0.1 part per million (ppm). Meliacin limonoids occurring in the seeds areazadirone, azadiradione, 17-epiazadiradione, nimbin, nimbinin, gedunin, vepinin, meldenin, and nimbolin (56). The insecticidal properties of these have not been investigated in depth (29). The efficacy of azadirachtin against insect pests native to the United States (e.g., Japanese beetles, cucumber beetles, Mexican bean beetles, Colorado potato beetles, a number of stored product insects, aphids and scale insects, cotton bollworms, tobacco budworms, and fall armyworms) and other countries is discussed by Warthen (56), Schmutterer, et al. (48), Ladd, et al. (32), Warthen, et al. (57), Redfern, et al. (45), and Meisner, et al. (34). Salannin is also an effective feeding deterrent for house flies (58) and several cotton pests in Israel (34).

Extraction: Neem seed extracts that are effective against insects have been prepared with hexane, ethyl ether, acetone, ethanol, and methanol (21,26, 54). Although the active compounds are only slightly water soluble, Indian farmers have used water to prepare spray solutions that prevent insect damage to tobacco (3). A procedure has been developed by scientists in the U.S. Department of Agriculture (54) for isolating azadirachtin of greater than 90 percent purity from ground neem kernels in 0.018 percent yield. The dry kernels are extracted first with hexane to remove largely inactive oil, then with acetone. The extract is chromatographed on Florisil and then by open-column liquid chromatography on Phase-bonded C-18 Hi-Flosil and μBondapak C-18 high performance liquid chromatography.

Salannin may be isolated from the kernels by extracting with 95 percent ethanol, partitioning the extract between methanol and hexane, and subjecting the methanol-soluble portion to column chromatography ondiatomaceous earth followed by chromatography on Florisil and high performance liquid chromatography of the active eluate on μBondapak C-18 (58).

Cultivation: Neem is a fast growing, sturdy tree that can be established without irrigation in hot and dry regions with annual rainfall of 500 mm or less. It grows well on shallow, stony, or sandy soils where agricultural crops have low yields, despite the application of fertilizers, or fail altogether. It thrives on dry, stony, and shallow soils with a waterless subsoil or in places where there is a hard calcareous or clay pan near the surface. The extensive roots of neem have the unique physiological capacity to extract nutrients from highly leached, sandy soils (42).

The neem tree has a wide range of possibilities for economic development, especially in arid zone countries. Two neem trees from Malaysia and one from Africa are growing well in Miami, Fla., at the USDA Horticultural Research Station and the Fairchild Tropical Garden, respectively. Neem plantations are abundant in northern Cameroon, Nigeria, and Gambia in Africa; in India; and in Cuba, Barbados, Honduras, and Antigua. The current policy of the U.S. Agency for International Development (AID) is to reduce the dependence of developing countries on imported pesticides. The U.S. Peace Corps is encouraging the mass cultivation of neem trees in Cameroon and Gambia. USDA has initiated a program to develop neem as a commercial crop in Puerto Rico and the U.S. Virgin Islands (21). It is envisioned that neem could be grown effectively where other agricultural crops are unproductive or present a severe erosion hazard.

Constraints: Although dry neem seeds are available commercially on the open market in India, these seeds do not ordinarily germinate. Under ordinary circumstances, neem seeds do not retain their viability for long; 2 weeks is probably the upper limit. Green (ripe) seeds, however, do germinate well in sand and a sand-sterilized soil-cachaza mixture. Germination is improved if the inner shell is removed before planting to expose the embryo. Since the complicated molecular structure of azadirachtin probably precludes its synthesis, it is fortunate that practical methods are available for isolating azadirachtin.

Azadirachtin formulations used to treat growing field crops are subject to photodegradation by sunlight. Acetone solutions of this compound exposed for 7 days show more than a 50 percent reduction inactivity; exposure for 16 days destroys the compound. Present research is aimed at preventing such photodegradation (51).

Neem seed oil has an unpleasant garlic-like smell, and the problems of deodorization, refining, and purification in large-scale industrial production have yet to be solved. Treating the oil with alcohol separates most of the odoriferous fraction, which can then be used in the manufacture of pharmaceutical preparations.

Another constraint mentioned by Radwanski and Wickens (42) is that: "Neem cannot be grown among agricultural crops since it will not tolerate the presence of any other species in its immediate vicinity and, if not controlled, may become aggressive by invading the neighboring crops."

The tree is tender to frost, especially in the seedling and sapling stages. In imperfectly drained soils, growth is poor and the taproot tends to rot.

Despite these constraints, cultivation and processing of neem are promising (35). The most work on commercial development of neem is being carried out in India by universities and government agricultural institutes which stress applied aspects and by USDA which is doing basic research on extraction and stabilization of the active compounds and methods ofapplication.

Heliopsis longipes (A. Gray) Blake

Common names: Chilcuage, peritre del pais, chilcuan

Family: Asteraceae

Description: H. longipes is a perennial herb with stems that are slightly woody and shrubby at the base. It grows to 20 to 50 cm and forms new shoots each year. Its few leaves are opposite, the flowers yellow, and the roots are slightly fleshy but fibrous.

Native range: Heliopsis grows natively in Mexico, from southern San Luis Potosi and northeastern Guanajuato and in mountainous areas south and southeast towards Alvarez. It is found at altitudes of 1,800 to 2,100 m in areas with annual rainfall of 370 mm. Its habitat is usually the oak-forest zone in sandy to clay soils.

Present and potential uses: Usually available in local markets in Mexico, the dried roots are used mainly as a spice to flavor beans and other foods. The tongue and mouth numb and burn when minute pieces are chewed. An extract of the roots is used for colds and pneumonia. Roots are chewed to relieve toothache. An alcoholic extract of the roots has been tested successfully by dentists as an anesthetic for tooth extraction (33).

In Mexico City, a local insecticide is prepared from *Heliopsis*. Some powdered root placed in the cattle's wounds made by warble flies kills the larvae. A petroleum ether extract of the roots is highly toxic to house flies, adults, and larvae of *Aedes* mosquitoes, body lice, melonworm and southern beet webworm larvae, bean weevils, squash bug nymphs, German and American cockroaches, black carpet beetles, and clothes moths (19). Spray formulations of the roots cause rapid knockdown of flying insects.

Active compounds: The active compound in root extracts was identified as the isobutylamide of (E,Z,E)-2,6,8-decatrienoic acid, which has been given the names "affinin" and "spilanthol" (23). It has been prepared synthetically (17) but in such a low yield that extraction is advocated for this plant.

Extraction: "Affinin" is obtained by extracting the dried roots with petroleum ether, partitioning the extract between this solvent and nitromethane, and filtering the nitromethane solution through a charcoal column. The pure compound is obtained in 0.4 percent yield by distillation as a pale yellow oil.

Cultivation: Wild plants have been transplanted successfully in rows and beds at four localities in Mexico at elevations of 1,800 to 2,400 m. The plants were dug with picks, most of the tops cut off, and the roots were trimmed. The rhizomes sprout readily at the nodes, so propagation by rhizome cuttings might be successful. The plant also can be propagated commercially by seeds. Roots of suitable size and quantity for harvest should be ready within 2 or 3 years after planting. Transplants under care grow better than wild plants (33).

Constraints: In spite of the succulent character of the roots, care must be used in transplanting. When exposed to the air, the roots dry out rapidly and shrivel within a week. Dried roots with bases of stems attached will not grow.

"Affinin" shows a marked tendency to polymerize in the pure state, although it can be kept almost indefinitely in solution with a hydrocarbon solvent such as benzene or toluene at 5° C. It has a burning, paralytic effect on the tongue.

Mammea americana L.

Common name: Mamey, mammy-apple

Family: Clusiaceae

Description: This is a handsome, conspicuous tree 12 to 18 m tall with shiny, leathery oval leaves; fragrant white flowers; and large globose russet-brown fruits 8 to 20 cm in diameter, with rough, bitter skin and orange apricot-flavored pulp surrounding one to four seeds. The trunk may reach 0.9 to 1.2 m in diameter.

Native range: Mamey is indigenous to the West Indies and tropical America.

Present and potential uses: An infusion of the edible fruits at 1 lb/gal of water is highly toxic to melon worm larvae both as a stomach and a contact poison, and also to fleas, ticks, and lice. The powdered seeds are very toxic to fall armyworms, melonworms, and diamondback moths, and in a water suspension are highly toxic to the larvae of several species of mosquitoes, American and German cockroaches, flies, ants, southern beet webworms, and southern armyworms. The leaves have been used for many years in Puerto Rico as a wrapping around the stems of newly set garden plants to prevent attack by garden insects. The powdered leaves are very effective as a stomach poison for chewing insects. The flowers are toxic to melonworm larvae (24).

The plant is widely cultivated in the French Antilles for a liqueur ("creme de creole") distilled from the flowers. The fruit is usually stewed or made into candles in Mexico. Because the wood is hard and durable, it is useful for construction. It is also used for cabinet making, as it is beautifully grained and takes a high polish. The resinous gum from the bark is used to extract chiggers from the feet. The sweet flesh of the fruit is eaten raw or cooked, and the juice makes a refreshing drink. The flesh normally adheres closely to the seeds, but seedlings grown in the Isle of Pines yield fruits in which the flesh separates readily from the seeds.

Active compounds: The principal insecticidal constituent, "mammein" or "mameyin," which comprises 0.19 percent of the seed weight, has been identified as 4-n-propyl-5,7-dihydroxy-6-isopentenyl-8-isovalerylcoumarin. The related compound 4-phenyl-5,7-dihydroxy-8-isopentenyl-6-isovalerylcoumarin, isolated from the fruit pulp, is also toxic to insects. An additional 24 coumarins isolated from the fruits are not insecticidal. All the coumarins are effective uncouplers of oxidative phosphorylation (8,24).

Extraction: Mammein is isolated by percolating the ground, large (40 g), egg-shaped seeds or fruits with petroleum ether, removing the solvent, dissolving the residue in acetone, and chromatographing on a column of alumina. The yield is about 180 g of mammein from 100 kg of seed.

Cultivation: The tree is cultivated for the edible fruit on Caribbean islands, and in Mexico, Central America, and South America. Several trees are growing at the Fairchild Gardens in Miami. It can be grown in Florida as far north as Palm Beach, but never has been grown successfully in California, probably because it will not stand more than 2 to 3 degrees of frost. The seeds germinate readily if planted in light, sandy, loam soil, and seedlings usually bear at 6 to 8 years of age. The tree is propagated by seeds and also by inarching and budding. The fruit ripens in summer.

Constraints: Although no serious attempt has been made at export or commercial use, there should be no difficulty in making this a commercial crop in southern Florida, Puerto Rico, or the Virgin Islands.

***Ocimum basilicum* L.**

Common names: Basil, sweet basil, garden basil

Family: Lamiaceae

Description: Sweet basil is an aromatic plant reaching a height of 60 to 70 cm. It is a glabrous or slightly pubescent herb with petiolate leaves and white or slightly purplish flowers.

Native range: O. basilicum is indigenous to France, Italy, Spain, Germany, Haiti, Indonesia, Samoa, Africa, India, Pakistan, and the Philippines.

Present and potential uses: Essential oil distilled from the fresh flowers or the entire basil plant is employed extensively as a flavor in confectionery, baked goods, condiments, and spiced meats and as an aroma in certain perfume compounds. It has antipyretic, antiseptic, diaphoretic, diuretic, and stimulant properties and, therefore, has been recommended for gastric disorders, malarial fevers, and skin diseases. The oil is an excellent repellent and larvicide for almost all species of mosquitoes and for mites and aphids (7,44). In India, freshly collected leaves or their ether or acetone extracts are rubbed on the back and arms to effectively repel mosquitoes for 4 to 6 hours. The essential oil is a powerful attractant for male fruit flies, *Dacus correctus*. Topical application of the oil inhibits growth and development of milkweed bugs, *Oncopeltus fasciatus* (6). The oil also has fungicidal properties.

Active compounds: Although not all of the repellent compounds in the essential oil have been identified, cineole, linalool, and methyl chavicol—which account for 3 percent, >50 percent, and 33 percent of the oil, respectively—are implicated (14). The fruit fly attractant has been identified as methyl eugenol. Two compounds, designated as "juvocimene I" and "juvocimene II," are responsible for the juvenilizing effects.

Extraction: The oil is extracted by steam distillation or enfleurage of the leaves or leaves and flowers. The yield depends upon soil fertility and seasonal conditions; cloudy or rainy weather immediately preceding the harvest reduces the yield, whereas bright sunny weather increases it. The highest oil yield obtained from any location was 49 kg/ha. Extraction of the leaves and/or flowers with solvents such as ether or acetone also produces oil that is repellent or toxic to insects. Since the many active components can be obtained readily from basil oil, their synthesis would be much less practical commercially.

Cultivation: The former Division of Drug and Related Plants of USDA experimentally cultivated the plant in Virginia for several years during the 1930's. The seed was imported from France and the whole fresh flowering herb was used for distillation of the oil. The plants grew rapidly on clay soil improved by mulching with pulverized stable manure. A highly fertile soil produces large succulent plants with low oil content.

Constraints: The seed will not germinate if planted at a depth of more than 0.6 cm. The cultivation of this annual in the United States should present no unusual difficulties. Since the crop is grown easily and good yields are obtained, the oil could be produced in many localities of the United States at reasonable prices (1).

***Tagetes minuta* L.**
(synonym: *T. glandulifera* Schrank)

Common names: Mexican marigold, stinking roger

Family: Asteraceae

Description: The plant is a glabrous branched annual attaining a height of 0.9 m or more and possessing clusters of fragrant orange-yellow flowers opening in August. It grows in any well-cultivated site, even in poor, rather dry soils.

Native range: T. minuta is native to Central and South America, especially Chile, but grows widely in Ethiopia, Kenya, and other areas of East Africa (especially in the highland areas) and northern India. It has been naturalized in the Eastern United States and South Africa, and occurs wild in sandy waste places of the Coastal Plain in North Carolina and in Spain.

Present and potential uses: The oil produced by the plant's seeds, leaves, and flowers is strongly repellent to blowflies and is useful in the tropics as a blowfly dressing. A dressing for sheep infested with blowfly larvae consists of an emulsion of 20 percent carbon tetrachloride, 5 percent *Tagetes* oil, 6 percent wool grease, and water. The emulsion breaks down soon after application, the larvae are killed within 1 minute, and the carbon tetrachloride and water soon evaporate. The leaves are used locally in Africa and India to repel mosquitoes and safari ants and recently have been found to kill mosquito larvae. The oil is more toxic to the larvae than DDT (4,36). The oil prevents molting, thus causing juvenilization in *Dysdercus koenigii* (46). It also possesses significant antitumor activity against the Lewis lung carcinoma in vivo (16). The oil possesses tranquilizing, hypotensive, bronchiodilatory, spasmolytic, and anti-inflammatory properties. *Tagetes* roots possess fungicidal and nematocidal properties (46).

Active compounds: Two of the mosquito larvicidal components of the oil have been identified as (E)-5-ocimenone (2,6-dimethyl-2,5,7-octatrien-4-one) (36) and the organic sulfur polyacetylenic compound *α*-terthienyl. The latter is also responsible for the nematocidal and bactericidal properties of the plant (4). The compound possessing juvenilizing properties has been identified as tagetone (2,6-dimethyl-5,7-octadien-4-one), which comprises 50 to 60 percent of the oil. These compounds have been synthesized. The oil also contains numerous organic sulfur-containing acetylenes, flavonoids, and carotenoids in addition to the terpenes ocimene, limonene, and estragole, which are used in perfumes and flavoring. The Japanese essential oil ("Ho-leaf oil") also contains tagetonol (2,6-dimethyl-7-octen-6-ol-4-one), which has been synthesized (55).

Extraction: The ground fresh leaves and flowers or other aerial portions are steam distilled, the distillate is extracted with hexane or petroleum ether, and the solution is dried. Evaporation of the solvent yields 0.5 to 1.0 percent of the yellow essential oil.

Cultivation: The seeds should be planted in late May in open, sunny sites. They germinate rapidly.

Constraints: Although several of the pesticidal components of *Tagetes* oil have been prepared synthetically in the laboratory, the synthetic methods involve multistep processes, which sometimes do not give the desired geometric isomers, and yields are poor. However, large-scale cultivation of the plant should pose no insurmountable difficulties, and the oil, which is easily obtained by distillation, can be used for pest control and as a source of pesticidal and medicinal compounds.

Recommendations

Although all of the seven plants discussed in this report are potential candidates for crop development and commercialization, the neem tree is by far the most likely to succeed despite the constraints mentioned. As a broad spectrum pesticide, neem is unsurpassed among the known insecticidal botanicals, both in the number of pest insects affected and the extremely small amounts required to reduce crop damage and cut down on the amounts of synthetic insecticides necessary. The leaves repel insects; the twigs are used as antiseptic toothbrushes; the seed oil is used for illumination and soapmaking; formulations of the seeds have powerful insect repellent, toxicant, feeding deterrent, and growth inhibiting properties; the oil-free seeds make an excellent fertilizer; and the timber, which is resistant to termites, is useful for home and furniture building. Furthermore, both the leaves and seeds contain compounds with considerable medicinal activity. Neem extracts, as well as azadirachtin and salannin, have no apparent mammalian toxicity, are not mutagenic, and are not phytotoxic at the concentrations normally used to control insects. The systemic properties of neem formulations are a definite advantage.

The neem tree begins to bear fruit in its fifth year and may live for over 250 years. It is easy to grow and requires virtually no extra care by the farmer. One tree produces 30 to 50 kg of seeds per year. Thirty kg of seeds yield 6 kg of neem oil and 24 kg of neem cake. The market price for neem oil in India is approximately $1 per kg and for neem cake is less than 50 cents per kg. Over 14 million neem trees exist in India alone (47). Neem is a prime candidate for the establishment of cottage industries in India and East Africa. Neem trees grow abundantly in large areas of Asia, Africa, and the Caribbean. At the USDA Horticultural Research Station in Miami, several of the trees are thriving and 1-year-old seedlings obtained from pollination are already 1.5 m tall. Two-year-old neem trees are growing at the Escuela Nacional de Ciencias Forestales in Comaqua, Honduras. It is recommended that these efforts to develop neem as a commercial crop in the United States and Central and South America be assigned a high priority, implemented, and expanded as rapidly as possible.

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MARINE PLANTS: A UNIQUE AND UNEXPLORED RESOURCE*

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Introduction

The seas provided a suitable site for the early evolution of all life. Ever since plants and animals developed structures and mechanisms that enabled them to survive on land, terrestrial and aquatic plants have been exposed to different abiotic and biotic selective pressures. Marine plants, which, unlike terrestrial plants, have evolved and adapted to life in a largely stable but saline environment, have developed many unique chemical structures not found in terrestrial plants.

The photosynthetic plants in the sea represent the foundation of the marine food web. The oceans occupy 70 percent of the Earth's surface, and the marine plants are known to provide at least the same percentage of available oxygen through photosynthesis. Marine plants are represented both by seaweeds, macroscopic forms largely inhabiting the shallow-water coastal zones, and by phytoplankton, free floating, widely distributed unicellular marine plants. Although a few flowering plants (angiosperms) are abundant in shallow waters, the majority of marine plants are algae, typified by their lack of a vascular system which serves for nutrient transport. Although all are classified as algae, these plants have an amazing taxonomic diversity. Marine algae have been subdivided into at least 12 distinct phyla (16):

Macroscopic forms	
Rhodophyta	....the red seaweeds
Phaeophyta	....the brown seaweeds
Chlorophyta	....the green seaweeds
Cyanophyta	....the blue-green algae
Chrysophyta	....the yellow-green algae
Haptophyta	....*
Xanthophyta	....*
Microscopic, usually unicellular forms	
Bacillariophyta	....the diatoms
Prasinophyta	....*
Eugenophyta	....the green algae
Cryptophyta	....*
Dinophyta	....the dinoflagellates

*No common nomenclature exists for these algal phyla.

Because of the highly unique and specific colorations of these groups, the analysis of numerous photosynthetic pigments has become a fundamental feature of algal classification. While no precise estimate is possible, well over 100,000 species of marine algae are thought to exist in various marine habitats.

Biogeographically, marine algae live in all parts of the ocean, from the tropics to the poles. Seaweeds and the phytoplankton frequently are found in extremely high concentrations. Although precise figures are difficult to substantiate, the primary productivity of 1 acre of open, plankton-rich ocean may be twice as large as that of a Midwest corn field.

A Unique Chemical Resource

Marine plants have evolved unique and highly specialized biochemical pathways to adapt to their unique seawater medium and survival pressures (7). The marine environment is rich in halogens, mainly in the form of chloride and bromide salts. Other chemical entities, such as sulfate, are also found in high concentrations. Marine plants use these elements in biosynthetic processess to produce compounds such as halogenated terpenes, acetogenins and alkaloids which are unique to the marine environment (6).

Many marine plants have evolved toxins and deterrents to enhance their survival in the face of abundant and freely migrating predators. Even though the same evolutionary pressures have produced similar responses in terrestrial plants, the defensive chemicals from marine plants are novel and represent interesting new chemical species which are unprecedented in terrestrial sources, even in closely related terrestrial algae.

Other adaptations, such as the development of resistance to wave shock and motion, have resulted in the synthesis of complex polysaccharides (complex sugars) which act to reduce the surface tension of seawater. These constituents, too, are highly specific to marine algae and help illustrate the unique genetic compositions of marine plants in general.

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*Another paper on marine plant products was written for the OTA workshop by Ara der Marderosian of the Philadelphia College of Pharmacy and Science. Dr. der Marderosian's paper focused on the early stages of marine pharmaceutical development in the late 1960's and mid-1970's. The constraints that existed then in this field still are present today—namely, problems of procuring and screening plants and extracting, isolating and characterizing their active ingredients; lack of both an adequate number of trained personnel and a multidisciplinary approach; and inadequate patent protection. Dr. der Marderosian advocates increased collaboration between government and industry and more long-term support for marine plant products work.

History of the Early Use of Marine Algae

Many societies, particularly those in the Indo-Pacific region and Asia, have developed important uses for marine algae (2). The most significant example is the use of various benthic seaweeds, such as *Porphyra* spp. and *Laminaria* spp., as food or food supplements. Such delicacy items as "Nori," and "Wakami" have become integral features of most diets in Japan. Shortages of these seaweed products have spawned intense aquaculture activities; for example, well over 18,000 MT of "Nori" are produced each year. A unicellular phytoplankton is harvested in several coastal regions in Thailand and used as the basis of a thick fish broth. The algae generally are not considered highly nutritious foods, but provide a broad base of mineral nutrition and roughage in the diet, and perhaps are most important for flavoring fish and rice dishes.

The classical use of marine algae as animal fodder and soil manure in northwest Europe has withstood the test of time. Marine algae, particularly that stranded on the beach after a storm, is collected and fed directly or after drying to sheep and cattle or applied on fields at rates of 56 to 67 MT/ha (25 to 30 tons/ac) as manure. This green manuring has been particularly useful on potato fields in the British Isles.

As man has become more aware of the unique chemical composition of marine algae, numerous additional products have been developed. A classical use for seaweeds has been the extraction of halogens and potash. Brown algae were used for several decades as the major source of iodine, and the red seaweeds were used on a few occasions for the derivation of bromine. The Pacific coast of America between 1910 and 1930 was the site of a flourishing potash industry based on the high potassium concentrations found in local brown algae.

It is not surprising that a wide variety of lesser known uses of marine algae also evolved. Numerous species of marine algae are used in China as herbal medicines to treat many maladies, ranging from intestinal problems to sunstroke. In addition, the gelling properties of aqueous extracts of numerous algae have been used in a host of food-related applications.

Modern Use of Marine Algae

The classical uses of marine algae as sources for elemental halogens, potash, and crude food thickeners largely were curtailed by the mid-1900's as other, more cost-efficient sources were developed. But also during this period, many currently used algal products, particularly algal polysaccharides, became established. A well-established industry in the United States now harvests marine algae (seaweeds) and extracts agar, carrageenan, and alginate. Agar is a sulfated polysaccharide (a polymer of the simple sugar galactose) found in many species of the red algae *Gelidium, Gracilaria,* and *Pterocladia.* This product is used mainly in the specialty food industry as a gelling agent and thickener, but also is used, among other things, as a biochemical adsorbent and as a culture and nutrient medium for bacteriological research. Agar is also a major nutrient medium for the industrial production of antibiotics.

Another specialty polysaccharide, carrageenan, is extracted routinely from red algae of the general *Chondrus, Gigartina,* and *Eucheuma.* This product also is a polymer of the simple sugar galactose, and its major applications resemble those of agar but are more widespread within the food industry. A complete description of the diverse applications of agar and carrageenan are given by Chapman (2). Polysaccharides derived from red algae support worldwide industries that produce about 18,000 MT per year at a total market value of about $200 million.

The brown seaweeds are also prized for their polysaccharide components, particularly alginate. Alginate is a mixed mannuronic and guluronic acid polymer comprising 20 to 30 percent of the overall composition of numerous brown seaweeds (particularly the so-called "kelps"). This polysaccharide represents a major worldwide industrial product generally prized for its thickening properties (e.g., in paints), emulsion stabilization properties, and gelling characteristics. Agar and carrageenan are far superior to alginate for use in foods, but alginates are particularly valuable for incorporation into industrial products and processes.

Even though the majority of the products derived from marine algae come from the readily collected macroscopic forms, several products are being produced by the culture of unicellular forms. The green alga *Dunaliella,* for example, recently has been established in mass culture as a commercial source for glycerol (glycerine) and the orange pigment beta-carotene. Glycerol is used industrially for numerous purposes, including in the manufacture of solvents, sweeteners, printing ink, antifreeze, shock absorber fluid, etc. Leffingwell and Lesser (12) have cited 1,583 different uses for glycerol, including the production of dynamite. Beta-carotene, the precursor to vitamin A, is used to impart color and provide vitamin A in animal feeds and human foods such as margarine. It is also used as a sunscreen agent.

Several algal species have been used consistently in the biomedical sciences. In particular, the red algae *Digenia simplex* and various *Chondria* species have been exploited in Asia for their content of effective anthelmintic drugs (to control intestinal parasites). The seaweeds' active components, kainic acid and domoic acid, were found to be relatives of simple amino acids, and they now are extracted, purified, and marketed as drugs in Asia. No other examples of successfully algae-derived pharmaceuticals exist, but there certainly is a great potential for further development in this area.

Development of Marine Algal Resources

The potential for developing a wide variety of commercial products from marine algae is great. As the supply of fossil fuels decreases, it will be essential to replace them with living or renewable resources. Even though relatively little **basic** chemical research has been performed on marine algae, it now seems clear that mass culture techniques, both in the ocean itself and in controlled coastal facilities, have great potential to provide industrially significant quantities of marine algae. As a result of funding from the Department of Energy (DOE) through the Solar Energy Research Institute (SERI) and several other agencies, scientists are learning of the nutrient and light requirements for effective algal growth. Marine algae probably will be a focus of considerable attention over the next decade as we investigate new resources for both energy and industrial product development.

Although relatively few algal products have been developed successfully by industry, the potential for the discovery and development of a plethora of unique new products seems unlimited. A few of the most notable areas for exploitation in the near future are summarized below.

Marine Algae for Biomass Conversion

Work already has begun to assess marine and other euryhaline algae as basic resources for biomass, with the expectation that through fermentation biomass can be converted easily to methane gas, ethanol, and other useful chemicals. A major concern is discovering plant sources that are easily grown in relation to their nutrient requirements, are highly efficient photosynthetically, and will yield readily digestible organic matter. At least the majority of these criteria are met by numerous species of macroscopic and microscopic algae. Algae are efficient photosynthetically and are cultured conveniently in the open ocean, ponds, or controlled (chemostatic) culture vessels. A major problem in algal biomass conversion lies in effective fertilization of cultured seaweeds and in cost-efficient harvesting of unicellular algae. Biomass conversion processes of any type are not cost efficient within the current economic structure. However, technology should continue to be developed so that resources and knowledge will be available for implementation when needed at a future date.

Pharmaceutical Development

The history and development of the modern pharmaceutical industry are based upon the extraction of biologically active substances from terrestrial plants and microorganisms. As human diseases change and pathogenic bacteria become resistant to established antibiotics, it becomes exceedingly important that new pharmaceuticals are available to reduce human suffering. As mentioned earlier, kainic acid, an anthelmintic drug in the Orient, was the first example of a useful drug extracted from marine algae (14). Few complete biomedical investigations have been performed on marine algae. Historically, biomedical applications of alginates and other algal polysaccharides have been clearly emphasized. This subject has been reviewed recently in an edited volume entitled "Marine Algae in Pharmaceutical Science," by Hoppe, Levring, and Tanaka (10). Although numerous uses for algal polysaccharides have been established, the majority of applications involve use of their physical properties rather than their physiological activities. A surprising percentage of algal polysaccharides, however, show antiviral activity. This area of drug development is of current interest. Extracts of red seaweeds from the family Dumontaceae, particularly the extract of *Constantinea simplex,* contain a specific and potent antiviral substance against *Herpes simplex* virus (4). The incidence of disease in the United States attributed to *H. simplex* has reached epidemic proportions.

The macroscopic seaweeds (red, brown, green, and blue-green algae) all possess structurally unusual, biologically active metabolites. Compounds that show impressive antibiotic activities (5,18), and a number of unique metabolites that show impressive cytotoxicities have been isolated from algae (9). The brown algal metabolite stypoldione (from *Stypopodium zonale*), for example, is a potent cancer cell cytotoxin which operates through a novel mechanism (11). Few comprehensive studies of microscopic algae have been reported, but there are several reports of antimicrobial activities (1,3). In addition, numerous phytoplankton species, such as *Gymnodinium breve, Gonyaulax catanella, Gonyaulax tamarensis, Prymnesium parvum*, inter alia, are known to produce the powerful toxins brevetoxin-B (13), saxitoxin (17), and prymnesin (15). In general, however, almost no information exists on the pharmacological potentials of the tens of thousands of microscopic plant species in the sea. This is due mainly to the difficulty in purifying a single species of unicellular algae and growing it for biomedical studies. This author is convinced that much could be learned from just such a dedicated effort.

Although a single algae-derived product exists, the slow rate of developing new marine pharmaceuticals clearly can be linked to the limited involvement of the major pharmaceutical companies. U.S. companies do not have a well-defined "entry" into this exploitation, and their lack of confidence is self-perpetuating within industry. Unlike any activity these industries have undertaken, marine explorations involve marine biological and oceanographic expertise, and the proper interface for this education has not existed. In addition, marine biological laboratories in the past have not employed scientists possessing capabilities in biomedical areas. The tide is changing, however, and major programs have developed under the auspices and support of the Department of Commerce's Sea Grant Program. The Sea Grant effort in biomedical development is a perfect blend of academic and industrial (basic and applied) research that is yielding fruitful results. The Sea Grant project, "Marine Chemistry and Pharmacology Program," at the University of California, for example, has discovered over 75 pure compounds with potential biomedical use and they have emphasized a collaborative effort with the pharmaceutical industry. This latter collaboration is the vital link to ensure that basic marine research finds its way to the industry that is *capable* and *interested* in developing new products.

Other governmental agencies have been involved to a more limited extent in marine biomedical development. For example, the National Cancer Institute has dedicated significant resources toward the isolation of new antitumor drugs. Here again, the need to involve basic marine scientists to locate, identify, and quantitate suitable marine species for study was underemphasized, and considerable difficulties (which affected output) were encountered.

The prospect for future development in this area is heavily underscored by the unique nature of marine-derived natural products. Based upon current chemical studies, it is clear that a wealth of novel structures exists in marine plants, and future biomedical studies of these compounds should prove highly productive.

Agricultural Chemicals

The use of naturally occurring compounds to control pests forms the basis of the agrichemical industry. For example, pyrethrins, insecticidal components isolated from pyrethrum, a daisy-like flower of the chrysanthemum family, and their synthetic derivatives continue to dominate agrichemical use. Many synthetic pesticides are halogenated compounds. Since halogenation is a natural process in marine plants, the compounds produced are likely to possess agrichemical activity. Only a few studies have been completed, but initial collaborative investigations indicate considerable promise. Of twelve purified algal metabolites thoroughly assessed in herbicidal and insecticidal bioassays, nine showed some activity, and one was nearly equivalent to DDT in insecticide activity (8).

Here again, the success in developing marine algal agrichemicals lies in developing a close relationship between academic and industrial research. A limitation on commercial development of marine extracts is that little government funding is available outside of the U.S. Department of Agriculture. Agricultural research funding should be expanded in the United States to include a greater component of academic research.

Food and Food Products

In addition to providing agar, carrageenan, and alginate, marine algae are recognized sources of triglycerides (many species are up to 20 percent triglycerides) which are used as cooking oils, and of numerous useful food products, such as hexose sugars and amino acids. Although seaweeds usually are low in protein, many phytoplankton are rich protein resources. Exploitation of protein-rich blue-green algae already has begun through the increased interest in *Spirulina* as a health food. *Spirulina* clearly is not the only algal species to qualify as a suitable food, and particularly the blue-green algae (many of which are nitrogen fixing) hold great promise for providing new protein resources. The American Medical Association emphasizes that good cardiovascular health can be achieved by reducing one's intake of animal protein, a protein source high in saturated fats. As society becomes more conscious of better health habits, there likely will be a shift toward plant protein sources, and a supplementary resource will be necessary.

Enzymes

The more we learn of the functions and behaviors of enzymes, the more enzyme technology is being applied to industrial processes. Marine enzymes, while almost completely unknown, could be used beneficially. The industrial process of halogenation to produce brominated and chlorinated chemicals is costly, due to the energy needed to activate bromide and chloride salts to their reactive levels. Enzymes perform this process in marine algae naturally; thus in principal, marine haloperoxidase enzymes could be used industrially. Hager and his associates (19) have successfully purified the marine halogenating enzyme and illustrated its behavior with numerous substrates.

Industrial Chemical Feedstocks

As oil reserves dwindle, the concept of seeking industrial chemicals from renewable plant sources no doubt will be considered seriously. We will need to turn to plant species that are readily cultured, have high photosynthetic rates, and contain hydrocarbon resources that somewhat resemble those found in crude oil. While an "oil-analog" will not be found, numerous examples of marine algae (both macroscopic and microscopic) produce mainly linear hydrocarbons. Species are available that could be cultured to yield hydrocarbon mixtures which could be used as diesel fuel without further purification. Linear alkanes and alkenes are virtually ubiquitous in marine algae, and these compounds could be converted (via catalytic cracking processes) to smaller molecules which form the basis of the modern plastic industry. Marine algae also have been reported to contain more unusual substances, such as low-molecular-weight sulfides and amines, as well as industrial precursor molecules, such as acrylic acid used in the production of plastics and in dentistry (1).

Notwithstanding the work on agar, carrageenan, and alginate, phytoplankton, in general, have been virtually unexplored for their polysaccharide components. A great need exists in this field to develop products with specific properties not found in existing saccharides. It is highly conceivable that the thousands of species of unicellular algae would yield new and important products.

Collection v. Aquaculture?

Marine plant development, whether dealing with the derivation of pharmaceuticals or industrial or food-quality chemicals, must be planned in relation to the most effective source of raw algal materials. Massive collections of natural seaweed populations conceivably could be made. While possible, this generally is unreasonable because limited numbers of species are found in abundance. Small volume products, such as a specialty pharmaceutical, could be developed from naturally occurring populations, but, in general, effective use of marine algal resources must be coupled with mass culture technology. Unicellular algae, in pure form, could not be collected so must be cultured under controlled physical conditions. Hence, marine algal resources development must be closely aligned with modern advances in algal mass culture.

Mass algal culture and product derivation should also be developed keeping in mind multiple product development. The algal resources that should be considered for development are those that produce more than one marketable product. Such is the case with *Dunaliella;* it yields beta-carotene and glycerol. This can be extended further to include the possible isolation of lipids (hydrocarbons, triglycerides, amines, etc.), the simultaneous extraction of water-soluble polysaccharides (products analogous to agar, etc.,) and, finally, the hydrolysis or digestion of the remaining material to produce either protein supplements or crude biomass for energy conversion. Multiple product use will be imperative from the economic viewpoint to offset the relatively high production costs.

Problems and Approaches Toward Developing Marine Algal Resources

A basic problem in considering development of marine algal resources is that there has been insufficient research on potential products from algae. Although a significant number of chemical investigations have been conducted on seaweeds, there have been few on unicellular algae. Many drug candidate molecules are known, but to date few have been screened as carefully as either pharmaceuticals or agrichemicals.

The cart has come before the horse to a certain degree in this field. Considerable resources are being devoted to developing algal culture technologies in marcroalgae and the unicellular species. However, in most cases these studies are not predicated on a solid knowledge of subsequent product development, but rather on broader concepts, such as algal biomass and energy conversion. The time has come to inititate tedious and costly long-term investigations of the chemical composition of marine algae, particularly the almost chemically unknown unicellular forms. Once a framework of sound composition information becomes available, decisions on what to culture can be made confidently.

A significant problem lies in the poorly developed working relationships between government, universities, and appropriate industries. Government funding agencies have difficulty supporting applied research, particularly as it may benefit a single private enterprise. The university system finds its interface with industry strained by patent and proprietary information problems. Therefore, the proper line of basic to applied research, culminating in real product development, has yet to be achieved.

Renewable resource development with any plant resource will require close collaboration of the agencies mentioned above. This is particularly true in developing marine products because scientists who have basic research interests will need to be involved. Federal funding agencies, such as the Sea Grant Program (Department of Commerce), should be applauded for providing a structural prototype which fosters the university-government-industry interaction.

Biotechnological advance, particularly in the field of marine genetics, can be expected to have a sizable impact on our use of marine resources. Marine products and biochemical processes are unique, and this unique gene pool will be highly useful in future product development. The algal gene for agar synthesis, for example, in principle could be transplanted into a readily culturable nonmarine organism. These concepts, while futuristic, illustrate the value of the marine algae to yield a wide variety of unique products.

Conclusions

Marine algae represent a massive resource for product development based upon their unique genetic adaptations. To foster this development, however, a greater emphasis must be placed on basic research into chemical composition, genetics, nutrition, and reproduction. Further, mass culture technologies must be refined. Collaboration among governmental agencies that provide funding must be developed in a tripartite fashion with universities excelling in marine research and with new industries. As these components gel into a more directed exploration of marine algal resources, it seems likely that marine algal species will become major sources of future products.

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THE ROLE OF THE ALKALOIDS OF *CATHARANTHUS ROSEUS* (L.) G.DON (*VINCA ROSEA*) AND THEIR DERIVATIVES IN CANCER CHEMOTHERAPY

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Abstract

The search for useful foodstuffs, dyes, medicinal agents, and other materials from plants, animals, or minerals is as old as civilization itself. It should not be surprising, therefore, to learn that all pharmacological prototypes originate from one of these three kingdoms.

The alkaloids, nitrogen-containing plant bases, notwithstanding the advent of antibiotics and many valuable synthetic drugs, constitute an indispensable part of our medicinal arsenal. The manufacture of alkaloids comprises an important segment of the fine chemicals industry. Their production is steeped in tradition, and processes are usually so highly specialized that it frequently takes years to establish them on an economic basis.

The author has based his pharmacognosy research on plants having reported folkloric usage and/or recorded chemical content. After conducting appropriate literature surveys, 440 plants were chosen for study. One of the plants collected and investigated was the Madagascar periwinkle, then botanically known by three names—*Vinca rosea*, *Catharanthus roseus*, and *Lochnera rosea*. This plant was reported to produce several desirable biological effects. Folkloric usage cited the plant as possessing properties that lowered blood sugar, thereby making it a possible source of an oral insulin substitute. It also was reported to contain alkaloids. Related *Vinca* species were reported to contain alkaloids and to possess both neurosedative properties and properties that lowered blood pressure.

Once obtained, extracts from *Catharanthus roseus* elicited none of the reported biological activities. (Eventually, pure compounds were isolated which did possess the reported properties.) Submission to a cancer screening program showed a profound and reproducible activity against an experimental leukemia model designed to predict clinical activity against human leukemia. One particular alkaloid, leurocristine (vincristine), was isolated. It was effective in treating not only acute lymphocytic leukemia of childhood but a wide variety of human neoplasms as well. It has become the "common denominator" in most combination therapies, serving as the synchronizing agent.

Classical methods of isolation and purification were of no value in obtaining the active antitumor agents from *C. roseus;* new techniques had to be devised. Use of selective/differential extraction, coupled with column chromatography and the gradient pH technique, has resulted in the reported isolation of 74 alkaloids from mature plants and an additional 21 chemical compounds from immature plants. This research and the results thereof constitute a classic in the annals of pharmacognosy/phytochemistry. Collecting hundreds of thousands of kilograms of this plant material from the wild did not seem promising or reliable. As a result, the plant was cultivated on farms in India and Madagascar. Because a number of variables could seriously threaten the supply of this life-saving drug, the decision was made to attempt cultivation in the United States. This was achieved in Texas using modern growing and harvesting techniques.

To date, attempts for a total synthesis of the active antitumor alkaloids have not been successful. Synthetic modifications have produced active agents, none of which have yet replaced the parent compounds. The drug from *C. roseus* is one of many drugs obtained from renewable resources.

The important drug isolated from the Madagascar periwinkle is known scientifically as leurocristine, generically as vincristine, and is marketed by Eli Lilly & Co., the pharmaceutical house to which I assigned the patent, as ONCOVIN.

It had been an in-house concept that no anticancer agent would or could ever produce a profit for the marketing company. The reason was that cancer is a progressively fatal and emotional disease. (Diabetes can be placed in this category, yet the financial track record for insulin is substantial.) Pricing for the marketing of ONCOVIN was designed to recover research and development costs, not an unreasonable concept.

A company official was reported by William L. Laurence in *The New York Times* as saying that "it will market the periwinkle chemicals at a price calculated to yield no profit to the company." Nevertheless, ONCOVIN became the highest percent profit item in the Lilly product line, carrying the relatively insignificant cost-of-sales of 12 percent. ONCOVIN provided an annual profit of several tens of millions of dollars.

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*Previously with Eli Lilly & Co.

It has been estimated that the world contains 500,000 to 750,000 higher order plants, less than 10 percent of which have been even cursorily investigated. The research success potential seems enormous. However, judicious plant selection must be coupled with appropriate biological test systems. In view of the not-for-profit pronouncements of the company known to have a successful phytochemical screening program, is it any wonder that other domestic firms hestitate to venture into this seemingly risky endeavor?

Private enterprise in the United States usually has been factorily innovative. When this occurs, intervention by government or others is unwarranted. However, government should expose and correct monumental profiteering. Also, when industry refuses to do the job, the government should present a choice: either do it with our cooperation, or we will do it without you. We now stand at this juncture.

Natural plant products have served as the basis of man's medicinal arsenal since time immemorial. The history of herbal medicine in the treatment of disease coincides with the history of medicine, and indeed with the history of civilization itself. Literature citations are recorded for more than 3,000 plant species that have been used or recommended in various parts of the world for the treatment of cancer (15).

It has been only within the last 20 years that any product from a higher order plant has been successfully used in cancer chemotherapy. Oddly enough, the plant yielding these agents was not included in the above-mentioned list of 3,000 plants. The isolation of two complex alkaloids—vincaleukoblastine (VLB) and leurocristine (LC) from the pantropical plant *Catharanthus roseus* (L.) G.Don (*Vinca rosea* L.) (Apocynaceae)—initiated a resurgence of interest in this area. The success of leurocristine, termed a "miracle drug" (38), in treating acute childhood lymphocytic leukemia and a wide variety of other human neoplasms is well documented.

The following discussion will be restricted primarily to *Catharanthus roseus* compounds possessing demonstrated utility in the treatment of human neoplasms, and in a few instances to compounds considered to have some potential utility on the basis of antitumor effects in experimental animals.

The true botanical name for the Madagascar periwinkle is *Catharanthus roseus* (L.) G.Don (33). It has also been referred to as *Lochnera rosea* Reichb. and *Vinca rosea* L. While the former name has no nomenclatural validity, the latter does. A text has been devoted to a study of this genus (39). It is important to recognize that *Catharanthus* alkaloids are different from *Vinca* alkaloids and ensure that information is recorded under the appropriate name.

The Madagascar periwinkle, *C. roseus*, originally a species endemic to Madagascar (Malagasy Republic), is an erect, everblooming herb or subshrub with either pink or white flowers that now has a tropical distribution. It is cultivated as an ornamental plant in gardens throughout the world.

Independent interest in this plant was generated by reports of hypoglycemic properties of certain extracts (14). The observation by Noble, Beer, and Cutts (29) of a toxic depletion of white cells and bone marrow depression produced in rats by certain fractions of these extracts eventually led to the isolation of vincaleukoblastine (VLB) sulfate.* Svoboda and Johnson, while screening selected botanicals for experimental antitumor activity, observed in certain extracts and fractions a reproducible oncolytic activity primarily against P1534 leukemia, a transplanted acute lymphocytic leukemia, in DBA/2 mice. This finding eventually led to the isolation of leurosine (35),** a new dimeric alkaloid closely related in chemical structure to VLB. Subsequently, VLB itself was isolated from the extracts (21).

Extraction of the *Catharanthus* Alkaloids

As with any single plant constituent, the extraction of an alkaloid is an individual problem. While several standard techniques existed for preliminary extraction of crude plant materials and subsequent separation and purification of individual alkaloids, none of these were applicable to the specific alkaloids of *C. roseus*. Consequently, a new technique of "selective" or "differential" extraction had to be devised (app. I) (36).

This technique differed from the classical approach in that a measure of purification was effected during extraction by forming salts of the stronger bases in the crude drug on addition of an aqueous solution of a naturally occurring weak organic acid. Final purification of most of the alkaloids was accomplished by column chromatography on Alcoa F-20 alumina which was partly deactivated with 10 percent acetic acid. This methodology was responsible for the isolation of leurosine and VLB sulfate in a single purification step.

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*The United States Adopted Names Committee (USAN) has approved vinblastine as the generic name for this alkaloid. It is available as VELBAN, VELBE (vinblastine sulfate, Lilly).

**The USAN-approved generic name for this alkaloid is vinleurosine.

The major thrust of the Lilly investigation, however, centered around the early observation that certain fractions produced an unusually high percentage of laboratory cures. Neither leurosine nor VLB, nor any therapeutic combination thereof, was responsible for these cures. Eventually a gradient pH technique was devised which yielded leurocristine* and leurosidine,** the two alkaloids responsible for the observed cures (35).

Use of selective or differential extraction, coupled with column chromatography and the gradient pH technique, has resulted in the reported isolation of 55 new alkaloids in our laboratories and three others which were codiscovered by other investigators. To date, 74 alkaloids, three of which we have never encountered, have been reported as having been isolated from mature plants of *C. roseus*. In addition, studies related to alkaloid biosynthesis involving immature plants have yielded known monomeric alkaloids, derivatives thereof, and glycosides. A total of 95 distinct alkaloidal entities have been isolated from this plant (app. II-VII).

One of the basic prerequisites for the successful isolation of the oncolytic alkaloids from *C. roseus* was the availability of a biological monitoring system—i.e., the P1534 leukemia. The use of this experimental mouse tumor as an in vivo assay was unique to the Lilly Research Laboratories and has demonstrated how important it is to use strain-specific tumors in inbred animals and to select tumors that are naturally resistant to most clinically useful agents. This screening procedure can be of great value in detecting new agents with different chemical structures. Just as a compound has a spectrum of tumor specificity, so a tumor may be said to have a "spectrum of compound specificity."

Structures and Pharmacologic Activities of *Catharanthus* Alkaloids

The determination and proof of the various indole and dihydroindole alkaloids structures proved to be an organic chemist's dream—virgin territory involving new entities and heretofore unknown combinations of ring systems, particularly those containing the dimeric indole-indoline structure. It would be remiss not to cite the imaginative and elegant efforts of Gorman and Neuss in establishing the structures of VLB (app. VIII) and leurocristine (app. IX) (26). The eventual elucidation of the sterochemistry of these structures (24) has made it possible to follow a rational approach in studying structure-activity relationships in this series.

Leurosidine (app. X), the most experimentally active antitumor alkaloid of this group, is isomeric with VLB (27). The difference is in the indole ("upper") portion of the molecule; the hydroxy (OH) is attached to an adjacent carbon (41). The epoxide structure proposed for leurosine (app. XI) by Abraham and Farnsworth (1) has been accepted quite widely.

Yields of leurocristine are on the order of 0.0003 percent, the lowest yield of any medicinally useful alkaloid ever produced on a commercial basis. Because yields of VLB are considerably higher, it would be worthwhile to design an oxidative process to convert VLB into leurocristine. Although several laboratories have "proven" that this could not be done, the conversion was in fact accomplished by a method using chromic acid oxidation at −60° C (22).

While derivatives of alkaloids from higher order plants seldom, if ever, possess more therapeutic activity than the parent compound, any decrease in toxicity or side effects can be a valuable contribution. One compound, desacetyl VLB, 4-(N-N-dimethyl-aminoacetate), displayed excellent experimental antitumor activity and possessed far more benign side effects than those of VLB. Consequently, this compound was selected for clinical testing (5). While initial results seemed promising, two patients receiving prolonged therapy subsequently suffered from corneal and lens changes in the eye. Although a causal relationship was not definitely documented, clinical trial with this derivative was terminated (18).

N-Formyl leurosine (app. XII) has shown activity against a series of animal tumors. Some reversible white-cell suppression was observed in rats, but no signs of neurotoxicity were found in the limited data reported (32). The latest derivative to stimulate scientific interest in this area is desacetyl VLB amide (*Vindesine*)* (app. XIII), a compound selected from a group of VLB derivatives prepared by Gerzon and coworkers (8).

Vindesine was selected because, in testing against tumor systems both sensitive and resistant to VLB and leurocristine, its spectrum of activity more closely resembled that of leurocristine than that of VLB (37). Its acute LD_{50} dose in mice, 6.3 mg/kg, is between those of VLB and leurocristine. No evidence of neurotoxicity has been observed in chronic studies in mice, rats, dogs, cats, and chickens (40).

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*The USAN-approved generic name for this alkaloid is vincristine. It is available as ONCOVIN (vincristine sulfate, Lilly).

**The USAN-approved generic name for this alkaloid is vinrosidine.

*The USAN-approved generic name for this compound is vindesine.

It is a matter of record that minor molecular modifications in the basic dimeric moiety can produce dramatic differences in dose-limiting toxicity. Preliminary clinical studies validate this premise; vindesine's dose-limiting toxicity involves both bone marrow and neurological toxicity, thereby placing it between VLB and leurocristine.

The dimeric *Catharanthus* alkaloids represent a new class of oncolytic agents. Attempts have been made to study their effects on various biochemical reaction sequences to determine their mode of action. However, the mechanism of the action of these compounds is still not clearly defined or understood.

These alkaloids appear to affect cell division in various phases and to varying degrees. This phenomenon has been observed in both in vitro and in vivo studies (30). Such inhibition can be observed in the absence of therapeutic response. VLB and leurocristine seem to elicit similar responses, as do leurosine and leurosidine.

Studies at the cellular level indicate that many pharmacologic effects of the *C. roseus* alkaloids can be attributed to their complexing with tubulin, the protein component of microtubules and the mitotic spindle. Substantial evidence indicates that microtubules are important for the substructure and probably the function of cell membranes. Of the agents studied, only these alkaloids produce microtubule crystals (7).

Data from various laboratories concerning the mechanism of action of the *Catharanthus* alkaloids appear to conflict in both the techniques and systems used (20,31). A definitive, concentrated effort at the molecular level, using drug-sensitive tumor systems, is clearly warranted.

The minor variation in the molecular structures of VLB and leurocristine has resulted in quite different spectra of tumor specificity in humans for these two alkaloids. In the relatively short time since their introduction into the clinic, the dimeric alkaloids from *Catharanthus roseus* have become some of the most valuable agents in cancer chemotherapy. They have proven to be useful as single agents in the palliative treatment of a number of advanced neoplasms, and more recently have played an important role in combination chemotherapy by heightening the action of other antitumor drugs.

The major use of VLB is in treating lymphoma, particularly in patients with Hodgkin's disease who are no longer candidates for high dose, extended field radiotherapy with curative intent. In single agent therapy, VLB rivals nitrogen mustard responses in 70 to 80 percent of patients.

VLB is highly effective in the treatment of testicular neoplasms. Objective responses also have been obtained, albeit with variable frequency, in patients with choriocarcinoma, neuroblastoma, Letterer-Siwe disease (histiocytosis X), and metastatic breast cancer.

The dose-limiting side effect of VLB is bone marrow depression. Temporary loss of hair and constipation are common.

As for vincristine, Taylor (38) says: "Judged by the usual yardstick of time for the development of new drugs and their clinical acceptance by physicians, vincristine qualifies as a miracle drug, for it was only 10 years ago that work was begun on this compound. Except for the increased activity in the field of cancer research, the work on vincristine was not abetted like the work on the miracle drug penicillin by a World War. In spite of this, vincristine is held in high regard by cancer chemotherapists, and much is known of its toxicology, pharmacology, and clinical activity in the human being. The worldwide search for plants containing substances that may inhibit cancer owes much to the incredibly successful story of vincristine."

The most striking feature of leurocristine is its ability to induce complete bone marrow remission of 50 percent of children with acute lymphocytic leukemia. In combination with steroidal hormones, a 90-percent complete-response rate can be expected. It is also considered to be highly effective in the treatment of Hodgkin's disease, Wilm's tumor, and rhabdomyosarcoma, and is said to be somewhat effective in the treatment of choriocarcinoma, breast cancer, and primary brain tumors. Responses against carcinomas of the cervix, prostate, and kidney have also been reported (19). Despite their extremely great structural similarities, there appears to be no cross-resistance between VLB and leurocristine.

Because of its lack of white-cell suppression, leurocristine becomes an excellent candidate in combination cancer chemotherapy. Two to five drug combinations give higher response rates and more prolonged remissions than obtained from single-agent therapy. Furthermore, new clinical concepts involve synchronization of cells in metaphase and alteration of membrane transport by leurocristine as an approach to combination therapy.

The dose-limiting side effects of leurocristine are its neuromuscular manifestations. Prophylaxis of constipation is indicated. Temporary loss of hair is more frequent than with VLB and is dependent on dosage and duration of treatment.

Children tolerate leurocristine therapy better than adults. Some treatment centers limit the adult dose to a maximum of 2 mg per injection. Toxicity is usually reversible, although its manifestations may persist for several months.

The clinical experience with leurosine, both as the sulfate (2,13,23) and the methiodide (16), has been more limited than with VLB and leurocristine. The methiodide was used in clinical trials before the sulfate because it had greater experimental activity against P1534 leukemia. However, little therapeutic activity was noted, while severe side effects outweighed the transient tumor shrinkage observed in two patients (4).

In the case of leurosine sulfate, clinical activity was evident but at a much lower level than that of VLB or leurocristine. Leukopenia was less pronounced than with VLB, but was the dose-limiting toxicity.

Noble and coworkers (28) observed in tissue culture studies that leurosine lysed malignant cells better than VLB and leurocristine when the alkaloids were added to the culture as sulfate salts in saline solution. However, the lytic activity of leurosine was inhibited completely in the presence of adult human plasma, but not fetal plasma. It was noted that the inhibitory factor of plasma resided in the globulins of the adult human plasma. Obviation of this protein inactivitation in human patients has not been accomplished and represents a real clinical challenge.

If the clinical predictivity of the P1534 in vivo system can be considered valid, leurosidine would be the most effective *Catharanthus* alkaloid in humans. However, its yield from the plant is lower than that of leurocristine. In addition, dose-response studies with P1534 leukemia in DBA/2 mice indicate that the optimum dose for complete cures in 100 percent of the mice is 30 times that of leurocristine, or 7.5 mg/kg compared to 0.25 mg/kg. Sufficient quantities of leurosidine have never been stockpiled to allow for a comprehensive clinical trial. Clinical evaluation had been initiated several years ago (3), but because supplies were limited was halted before conclusive efficacy was observed. Transient responses and the appearance of some apparent neuropathy were noted in patients receiving high doses of the drug. It cannot be considered as having been adequately evaluated by current standards. Sufficient quantities would have to be provided by an alkaloid modification program, which has yet to be accomplished.

N-Formyl-N-desmethyl leurosine would not have been chosen as a clinical candidate on the basis of experimental antitumor activity in screening programs used in the United States today. However, it has been reported as producing complete remissions in acute leukemia and partial remissions in malignant lymphomas, chronic lymphocytic leukemia, and multiple myeloma (10,11). These preliminary clinical studies reveal no neurotoxicity and indicate well-tolerated effects on hemopoietic tissues, except for transient effects on mature cells of the granulocytic series. Personal communications regarding its clinical efficacy indicate that cardiovascular complications will preclude its utility as a single agent entity.

Desacetyl VLB amide (Vindesine) has been in Phase I clinical trial. In one study involving 32 adults with far-advanced neoplasia, it produced partial remissions in two of nine patients with acute leukemia, one of four with squamous carcinoma, and one of four with renal cell carcinoma. No responses were seen in patients with malignant melanoma, colorectal carcinoma, or several other types of advanced solid tumors. Sixty percent of the patients in this study previously had received *Catharanthus* alkaloid therapy (6). In a second study, minor responses were seen in acute lymphocytic leukemia, acute myelogenous leukemia, hypernephroma, lymphoma, and Ewing's sarcoma. No signs of neurotoxicity were observed in children (9).

A recent Phase II single agent study achieved two complete remissions and four partial responses in 21 patients with advanced breast carcinoma (overall response rate of 29 percent). Results in a pilot study involving patients with advanced multiple myeloma resistant to alkylating agents appeared to be promising. Phase II studies in non-small lung cancer showed frequent major objective responses (17).

In the adult patient, vindesine has myelosuppressive activity resembling that of VLB. While the neurotoxicity produced by vindesine is similar to that of leurocristine, it is less severe and does not progress even with continued therapy. Pharmacological studies indicate that vindesine has a larger volume of distribution, longer serum half-life, and lower rate of renal clearance than VLB, all of which may account for the longer duration of marrow suppression induced by this drug (25).

Cancer chemotherapy has evolved over the past 20 years so that it now ranks with surgery and radiation as a palliative, and in many instances curative, mode of treating malignant disease. Much of the improving efficacy of chemotherapy is the result of development of multiple drug regimens. Initially these drug combinations were derived empirically by selecting agents that had different mechanisms of action and showed as little additive toxicity as possible. This empirical approach has progressed in sophistication to the point where it is now even possible to use multidrug regimens that block different discrete segments of the cell cycle. The *Catharanthus roseus* alkaloids play an especially important role in these multidrug regimens. Now that chemotherapy is being developed to augment surgery on both a pre- and post-operative basis, the prognosis for many types of human malignancy appears increasingly bright.

Problems and Potentials

Many problems were encountered during the course of this research, and corresponding solutions were devised. A number have been described; others follow.

Supplying the hundreds of thousands of kilograms of raw material required per year could have become a monumental problem. Adequate supply of the natural plant material had to be maintained. Original work was performed on the whole plant. Determination that the desired alkaloids were found in the leaves allowed for stripping of the plant, thereby affording a healthier and more profuse regrowth. Collection from the wild eventually progressed to farm or plantation cultivation, allowing for greater control over growth.

In anticipation that politics would threaten what had been a reliable crude drug supply, experimental plantings were begun in the United States. New crop introduction is always risky. The economics involved are always of major concern. Hand collection and "native" wages are out of the question. Despite the risk, plantations were started in Texas; India and Madagascar had lost a viable cash crop. A forage harvester replaced hand labor and, a single planting was able to provide several harvests per season, surviving harvester-cutting with relatively rapid regrowth.

Periwinkle cultivation represents a renewable resource. The chemical complexities of the antitumor alkaloids have to date defied practical total synthesis. When realized, it certainly will require the ready availability of petroleum-derived starting materials.

The American pharmaceutical industry was built on and sustained by natural products from the higher order (chlorophyll-containing) plants. It is an enigma that little work in this realm is being pursued by U.S. industry, particularly since approximately 25 percent of new and refilled prescriptions from community pharmacies contain plant products (12).

There is no dearth of plants to be collected and screened for specific or general biological activity. Of the Earth's 500,000 to 750,000 higher order plants, less than 10 percent have been investigated phytochemically. The investigator has an almost unlimited choice for selection.

Success potential should be extremely high. However, one must select plants judiciously and must have appropriate biological test systems available for monitoring isolation and purification progress. Plant selection can be based on reported folkloric usage, but said usage must be rational in both an investigative and practical sense.

The use of *Catharanthus roseus* as an oral insulin substitute previously has been cited. Reports of usage against hemorrhage, scurvy, as a mouthwash for toothache, and for healing and cleaning chronic wounds (36) did not stimulate either scientific or pratical adrenalin. And yet, these uses could well prove valuable.

Selection of plants to be tested based on reported chemical constituents may also be useful. The author selected alkaloids for research, not only because of familiarity therewith but also recognition that most medicinal agents of plant origin fall into this category.

A third, and very valid, category for selection is a plant which never before has been investigated. This obviously represents the bulk of selective material. Here again, prudence must be exercised. Botanical and chemotaxonomic relationships must be considered.

The fact that major U.S. pharmaceutical houses are no longer engaged in pharmacognostical/phytochemical research, particularly as it relates to palliative/curative measures against human cancer, may well stem from the erroneous concept that any product would be a "not-for-profit" item. It may also stem from ignorance on the part of research administrators who conceive, and most certainly maintain, that antibiotics will treat or cure all ills, mainly those designated as "profits."

The marketplace has been extremely kind to the periwinkle alkaloids, particularly leurocristine (vincristine, ONCOVIN). It has become the highest percent profit item in the product line of Eli Lilly & Co., bearing the almost insignificant cost-of-sales of 12 percent. Yearly sales running into tens of millions of dollars indicate the absolute success of this natural product. Perhaps public pronouncements that the item was to be sold "at a price calculated to yield no profit to the company" misled other companies that were considering entering the field.

The greatest story **never** told could well be the search for an ethereal entity often referred to as "super leurocristine." This tentative title was bestowed upon it by virtue of experimental antileukemic activity. Typical leurocristine/leurosidine fractions exhibited activity on the order of three survivors at a dosage of 0.3 mg/kg. "Super" fraction activity was of the order of three survivors at 0.0009 mg/kg, representing a 300-percent increase in activity (or decrease in dosage).

Workup of "super" material failed to yield any new crystalline compounds. The press of readying leurocristine for clinical trial and subsequent marketing prevailed over investigative matters. Besides, equivalent material was being stockpiled for later investigation, thereby affording larger quantities for workup. Unbelievable as it seems now, and most certainly at the time, these stockpiled materials were discarded in an unsanctioned and misguided cleanup effort.

Because of processing changes which were constantly being initiated, no such "super" material could again be stockpiled. Efforts to repeat the original process for stockpiling purposes were denied, as certain cost projections for "experimental processing" were prohibitive. If the problem of human cancer were solved, the search for "super leurocristine" would probably be a matter of scientific semantics, but the problem has not been solved, and the challenge must be met.

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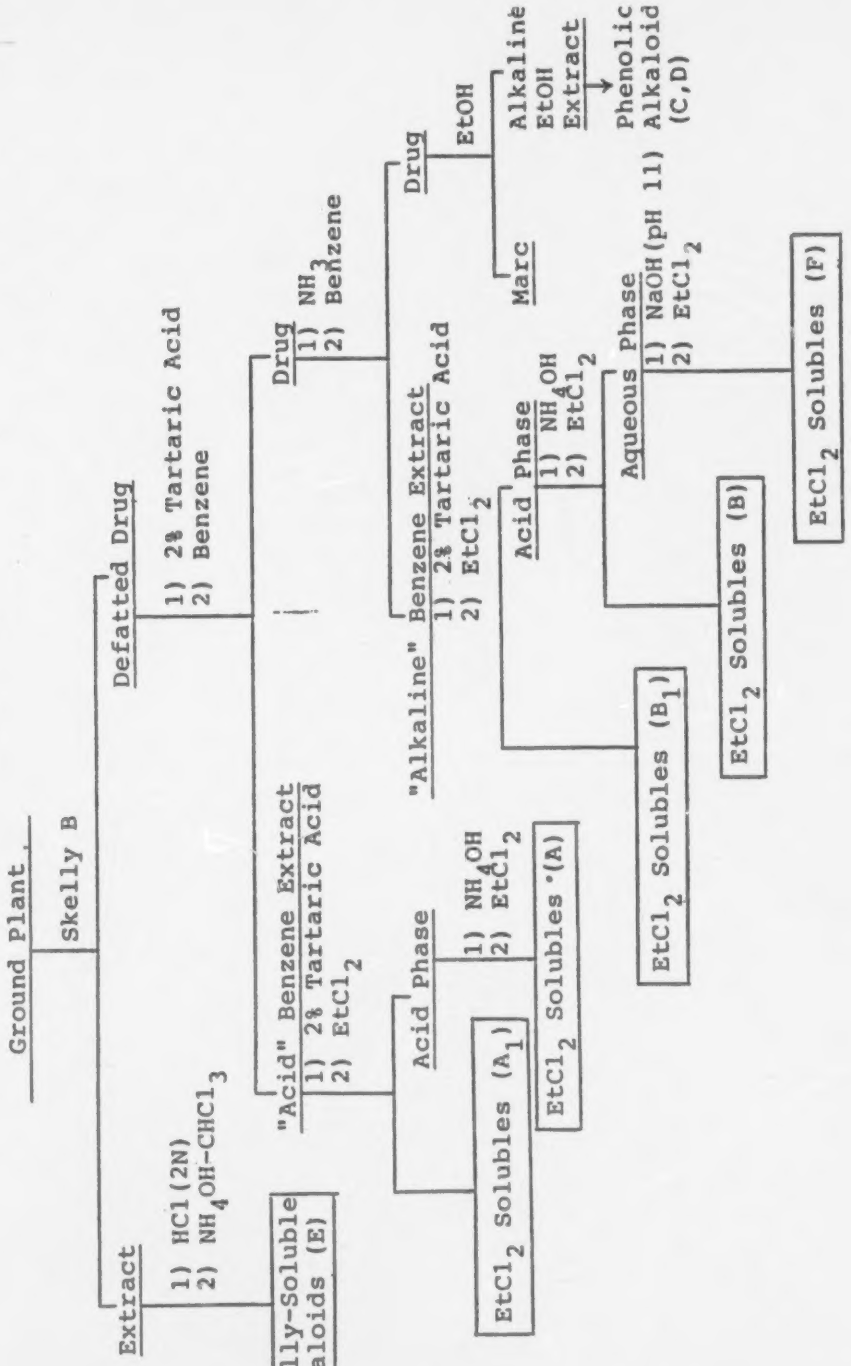
Appendix I.—Extraction Scheme


Ground Plant
Skelly B
Extract
1) HCl (2N)
2) NH4OH-CHCl3
Skelly-Soluble Alkaloids (E)
Defatted Drug
1) 2% Tartaric Acid
2) Benzene
"Acid" Benzene Extract
1) 2% Tartaric Acid
2) EtCl2
Acid Phase
1) NH4OH
2) EtCl2
EtCl2 Solubles (A1)
EtCl2 Solubles (A)
Drug
1) NH3
2) Benzene
"Alkaline" Benzene Extract
1) 2% Tartaric Acid
2) EtCl2
Acid Phase
1) NH4OH
2) EtCl2
EtCl2 Solubles (B1)
EtCl2 Solubles (B)
Aqueous Phase
1) NaOH (pH 11)
2) EtCl2
EtCl2 Solubles (F)
Drug
EtOH
Marc
Alkaline EtOH Extract
Phenolic Alkaloid (C,D)

Appendix II.—Alkaloids Previously Reported

Name	Empirical formula	M.P., °C
Ajmalicine	$C_{21}H_{24}N_2O_3$	253-254
Tetrahydroalstonine	$C_{21}H_{24}N_2O_3$	230-231
Serpentine	$C_{21}H_{22}N_2O_3$	156-157
Lochnerine	$C_{20}H_{24}N_2O_2$	202-203
Akuammine[a]	$C_{22}H_{26}N_2O_4$	258-260
Reserpine[a]	$C_{33}H_{40}N_2O_9$	264-265

Appendix III.—Monomeric Alkaloids

	Formula	pK'_a	M.P. °C	Source[b]
Indoles				
1. Alstonine[a] $(\cdot HCl)$	$C_{21}H_{20}N_2O_3 \cdot HCl$	--	281-282	Rb
2. Ammorosine	----	7.30	221-225	R
3. Catharanthine	$C_{21}H_{24}N_2O_2 \cdot H_2O$	6.8	126-128	L , R
4. Cathindine $(\cdot \tfrac{1}{2}H_2SO_4)$	----	7.25	239-245 (dec.)	R
5. Cavincidine $(\cdot \tfrac{1}{2}H_2SO_4)$	----	7.85	236-239 (dec.)	R
6. Cavincine $(\cdot \tfrac{1}{2}H_2SO_4)$	$C_{20}H_{24}N_2O_2 \cdot \tfrac{1}{2}H_2SO_4 \cdot \tfrac{1}{2}H_2O$	6.90	275-277 (dec.)	L , R
7. Dihydrositsirikine	$C_{21}H_{28}N_2O_3$	--	215	L , R
8. Isositsirikine $(\cdot \tfrac{1}{2}H_2SO_4)$	$C_{21}H_{26}N_2O_3 \cdot \tfrac{1}{2}H_2SO_4$	--	263.5	L , R
9. Pericyclivine	$C_{20}H_{22}N_2O_2$	--	228	L
10. Sitsirikine $(\cdot \tfrac{1}{2}H_2SO_4)$	$C_{21}H_{26}N_2O_3 \cdot \tfrac{1}{2}H_2SO_4$	7.6	239-241 (dec.)	L , R
11. Vinaspine	----	7.85	235-238	L
2-Acyl Indoles				
1. Perividine	$C_{20}H_{22}N_2O_4$	neutral	271-279 (dec.)	L
2. Perivine	$C_{20}H_{24}N_2O_3$	7.5	180-181	L , R
3. Perosine $(\cdot \tfrac{1}{2}H_2SO_4)$	----	7.60	219-225	L , R
Oxindoles				
1. Mitraphylline	$C_{21}H_{26}N_2O_4$	6.20	269-270	L , R

Appendix IV.—Monomeric Alkaloids

	Formula	pK_a'	M.P., °C	Source[a]
a-Methylene Indolines				
1. Akuammicine	$C_{20}H_{22}N_2O_2$	7.98	181-182	R
2. Lochnericine	$C_{21}H_{24}N_2O_3$	4.2	190-193 (dec.)	L
3. Lochneridine	$C_{20}H_{24}N_2O_3$	5.5	211-214 (dec.)	L
4. Lochnerinine	$C_{22}H_{26}N_2O_4$	----	168-169	L
5. Lochnerivine	$C_{24}H_{28}N_2O_5$	neutral	278-280	R
6. Lochrovicine	$C_{20}H_{22}N_2O_3$	4.50	234-238	L
7. Lochrovidine	$C_{22}H_{26}N_2O_4$	5.60	213-218	L
8. Lochrovine	$C_{23}H_{30}N_2O_3$	neutral	258-263	L
Dihydroindoles				
1. Catharosine	$C_{22}H_{28}N_2O_4$	----	141-143	L
2. Desacetylvindoline	$C_{23}H_{30}N_2O_5$	----	163-165	L
3. Maandrosine ($\cdot \frac{1}{2}H_2SO_4$)	----	6.90	160-173	R
4. Vincolidine	$C_{23}H_{26}N_2O_3$	5.45	165-170	L
5. Vincoline	$C_{21}H_{24}N_2O_4$	6.1	230-233	L
6. Vindoline	$C_{25}H_{32}N_2O_6$	5.5	154-155	L
7. Vindolinine (·2HCl)	$C_{21}H_{24}N_2O_2 \cdot 2HCl$	7.1	210-213 (dec.)	L
8. Vindorosine	$C_{24}H_{30}N_2O_5$	----	167	L
Miscellaneous				
1. Ammocalline	$C_{19}H_{22}N_2$	7.30	>335 (dec.)	R
2. Pericalline (Tabernoschizine) (Apparicine) (Gomezine)	$C_{18}H_{20}N_2$	8.05	196-202	R
3. Perimivine	$C_{21}H_{22}N_2O_4$	indeterminate	292-293 (dec.)	L
4. Virosine	$C_{22}H_{26}N_2O_4$	5.85	258-261 (dec.)	R

Appendix V.—Dimeric Indole-Indoline Alkaloids

		Formula	pK_a	M.P., °C	Source[a]
1.	Carosine	$C_{46}H_{56}N_4O_{10}$	4.4, 5.5	214-218	L
2.	Catharanthamine	$C_{46}H_{56}N_4O_9$	-	-	L
3.	Catharicine	$C_{46}H_{52}N_4O_{10}$	5.3, 6.3	231-234 (dec.)	L
4.	Catharine	$C_{46}H_{52}N_4O_9 \cdot CH_3OH$	5.34	271-275 (dec.)	L
5.	N-Demethyl VLB	$C_{45}H_{56}N_4O_9$	-	-	L
6.	Desacetoxy VLB	$C_{44}H_{56}N_4O_7$	-	-	L
7.	Desacetyl VLB ($\cdot H_2SO_4$)	$C_{44}H_{56}N_4O_8 \cdot H_2SO_4$	5.40, 6.90	>320 (dec.)	L
8.	Isoleurosine	$C_{46}H_{58}N_4O_8$	4.8, 7.3	202-206 (dec.)	L
9.	Leurocolombine	$C_{46}H_{58}N_4O_{10}$	5.05, 6.3	-	L
10.	Leurocristine	$C_{46}H_{56}N_4O_{10}$	5.0, 7.4	218-220 (dec.)	L, R
11.	Leurosidine	$C_{46}H_{58}N_4O_9$	5.0, 8.8	208-211 (dec.)	L, R
12.	Leurosidine $N_b{}^1$-oxide	$C_{46}H_{58}N_4O_{10}$	-	215-218	L
13.	Leurosine	$C_{46}H_{56}N_4O_9$	5.5, 7.5	202-205 (dec.)	L, R
14.	Leurosivine ($\cdot H_2SO_4$)	$C_{41}H_{54}N_3O_9 \cdot H_2SO_4$	4.80, 5.80	>335 (dec.)	R
15.	Neoleurocristine	$C_{46}H_{56}N_4O_{12}$	4.68	188-196 (dec.)	L
16.	Neoleurosidine	$C_{48}H_{62}N_4O_{11}$	5.1	219-225 (dec.)	L
17.	21^1-Oxoleurosine	$C_{46}H_{54}N_4O_{10}$	-	215	L
18.	Pleurosine	$C_{46}H_{56}N_4O_{10}$	4.4, 5.55	191-194 (dec.)	L
19.	Pseudovincaleukoblastine-diol	$C_{46}H_{56}N_4O_8$	-	-	L
20.	Rovidine ($\cdot H_2SO_4$)	----	4.82, 6.95	>320 (dec.)	L
21.	Vinamidine	$C_{46}H_{56}N_4O_{10}$	-	-	L
22.	Vinaphamine	----	5.15, 7.0	229-235	L
23.	Vincadioline	$C_{46}H_{58}N_4O_{10}$	-	-	L
24.	Vincaleukoblastine	$C_{46}H_{58}N_4O_9 \cdot (C_2H_5)_2O$	5.4, 7.4	201-211	L, R
25.	Vincathicine ($\cdot H_2SO_4$)	----	5.10, 7.05	> 320 (dec.)	L

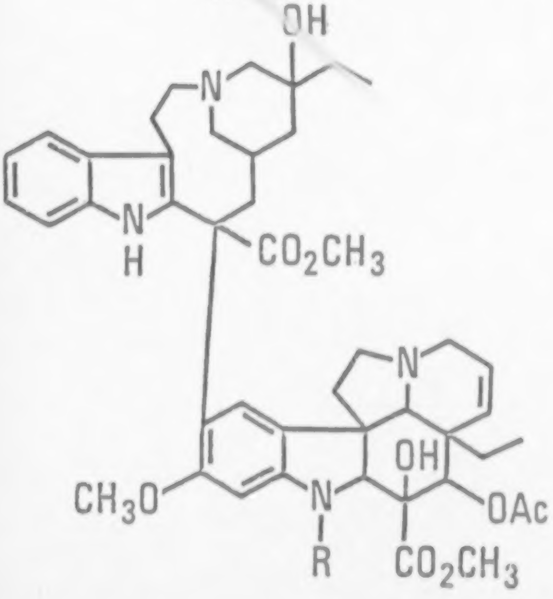
Appendix VI.—Miscellaneous Dimeric Alkaloids

	Formula	pK'_a	M.P., °C	Source[a]
1. Carosidine	----	indeterminate	263-278, 283 (dec.)	L R
2. Vincamicine	----	4.80, 5.85	224-228 (dec.)	L
3. Vincarodine	$C_{44}H_{52}N_4O_{10}$	5.8	253-256 (dec.)	L
4. Vindolicine	$(C_{25}H_{22}N_2O_6)_2$	5.4	248-251 (melts, recryst.) 265-267 (dec.)	L
5. Vindolidine	$C_{48}H_{64}N_4O_{10}$	4.7, 5.3	244-250 (dec.)	L
6. Vinosidine	$C_{44}H_{52}N_4O_{10}$	6.80	253-257 (dec.)	R
7. Vinsedicine	(Mol. wt. 780)	4.45, 7.35	206	S
8. Vinsedine	(Mol. wt. 778)	4.65, 7.0	198-200	S

Appendix VII.—Alkaloids Isolated From *C. roseus* From Biosynthesis Experiments

Alkaloid
19-Acetoxy-11-hydroxy tabersonine
19-Acetoxy-11-methoxy tabersonine
N-Acetylvincoside
Ajmalicine
Akuammicine
Catharanthine
Cathenamine
Coronaridine
Corynantheine
Corynantheine Aldehyde
4,21-Dehydrogeissoschizine
19-Epi-ajmalicine
19-Epi-vindolinine
Geissoschizine
Hörhammericine
Hörhammerinine
Isovincoside
11-Methoxytabersonine
Preakuammicine
Stemmadenine
Strictosidine lactam
Tabersonine
Vallesiachotamine
Vincoside
Vindoline

Appendix VIII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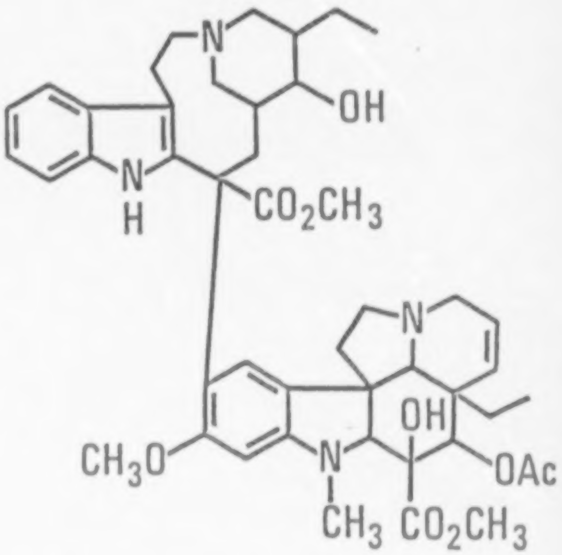
N
N
H
CO$_2$CH$_3$
N
OH
CH$_3$O
N
OAc
R
CO$_2$CH$_3$

Appendix IX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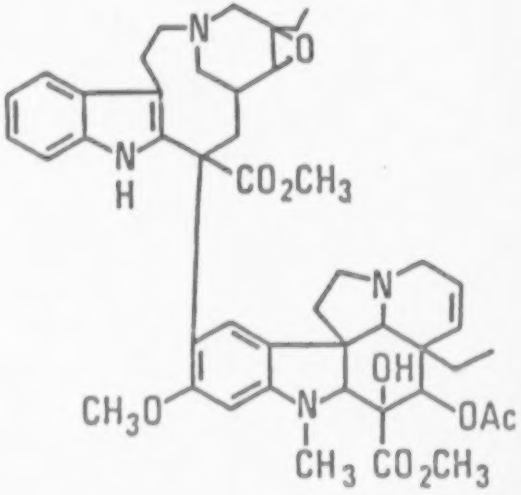
N
H
CO$_2$CH$_3$
N
OH
CH$_3$O
N
OAc
CH$_3$
CO$_2$CH$_3$

Appendix X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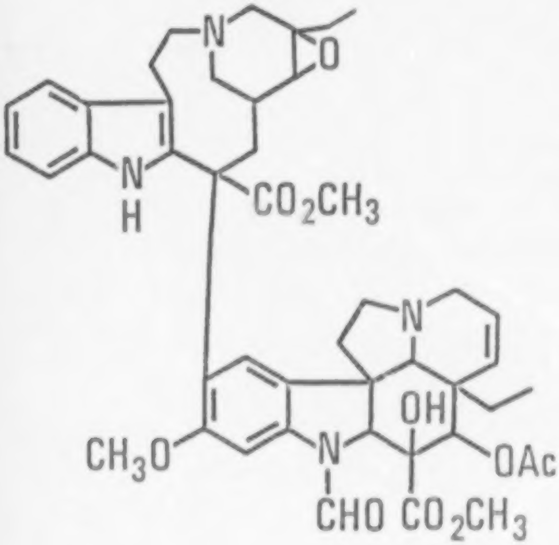
O
N
H
CO$_2$CH$_3$
N
OH
CH$_3$O
N
OAc
CH$_3$
CO$_2$CH$_3$

Appendix XI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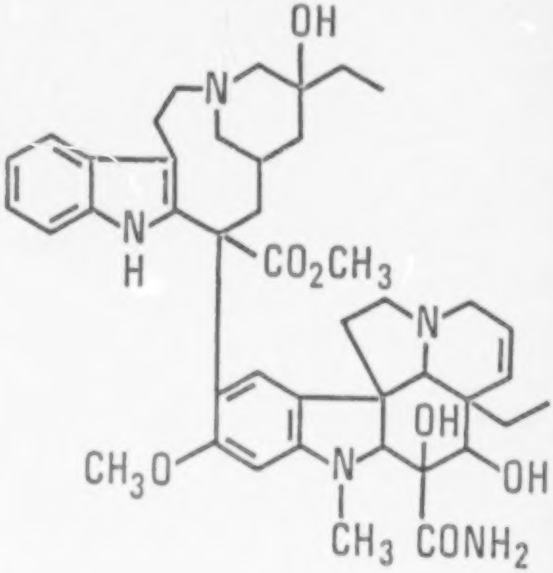
O
N
H
CO2CH3
N
CH3O
OH
N
OAc
CHO
CO2CH3

Appendix XII


OH
N
N
H
CO2CH3
N
OH
CH3O
N
OH
CH3
CONH2

STRATEGIC AND ESSENTIAL INDUSTRIAL MATERIALS FROM PLANTS THESIS AND UNCERTAINTIES

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Soil Conservation Service
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Strategic and Essential Industrial Materials

The United States depends on other nations for a broad range of materials and manufactured products important to U.S. industry. Among these are agriculturally produced plant substances and mined materials, including petroleum. This paper is concerned with products that are or could be agriculturally produced in the United States and used as industrial materials or as renewable replacements for petroleum as sources of feedstock in the chemicals industry.

Three of these industrial materials are classified by law as "strategic," meaning critical to our national defense. These are natural rubber, castor oil, and sperm whale oil. The Defense Production Act of 1950 as amended in 1980 (Public Law 81-774) requires that sufficient supplies of these materials be acquired and stored in the United States to meet national defense needs in case of war. The costs of acquisition, storage, and replacement are borne by the Federal Government, which must manage the stocks so they do not interfere with the marketplace for these commodities. Stockpiles are used only for meeting military needs and are not available to meet emergency civilian needs. "Essential" materials are those required by industry to manufacture products depended upon daily. Essential materials include the strategic materials, waxes, resins, oils, gums, newsprint, other items manufactured or extracted from plants, and replacements for petroleum used as feedstock in manufacturing synthetic organic chemicals, plastics, industrial coatings and paints, printing inks, surfactants, and synthetic fibers.

Thesis and Purpose of the Paper

This paper will present and discuss some of the policy issues related to use of U.S. land, capital, and labor to meet the Nation's long-term needs and to reduce dependence on other nations for strategic and essential industrial materials. The thesis is that the United States can move industrial dependence on a finite resource (petroleum) to renewable ones (agriculturally produced feedstocks).

Available Data

Comprehensive data on imports of agricultural commodities are available from the *Agricultural Statistics* series published annually by the Department of Agriculture (5). The United States International Trade Commmission provides comprehensive information on total imports of petroleum and on total domestic production of synthetic organic chemicals. Chemical data on plant extracts are found in publications of the Department of Agriculture, Agricultural Research Service's Northern Regional Research Laboratory (Center) at Peoria, Ill. The level of confidence in all these sources is high. Examples are shown in table 1.

Other data used in this paper represent estimates rather than "hard," quantifiable figures. For example, the total amount of plant material and various precursor chemicals imported for use in U.S. industry to produce essential industrial materials is not recorded and must be estimated. Similarly, although the total amount of petroleum imported is known, the amount that might be replaced by renewable sources of feedstock in manufacturing chemical products must be estimated. The best available estimates now are thought to be those made by research chemists in the Department of Agriculture. These are shown in table 2.

Much of the information presented in this paper is synthesized from papers published in refereed scientific journals over a period of 10 or more years, from monographs available from the Agricultural Research Service, and data collected by a task force of USDA's Science and Education Administration (SEA) personnel established to explore the USDA/SEA role in strategic and essential industrial materials research (7).

Lists of Imports for Which There May Exist Domestic Production Alternatives That Could Be Implemented In Ten Years

Table 1.—Agricultural Imports—1978

Product		Value of Imports ($ Millions)
Natural Rubber		$665.9
Vegetable Oils and Waxes		$458.0
Castor	$40.0	
Palm	$74.9	
Palm Kernel	$34.8	
Olive	$36.8	
Coconut	$228.9	
Natural Waxes		$9.3
Cocoa Butter		$96.1
Fibers (Other than cotton or jute)		$28.2
Drugs (Agricultural)		$137.1
Essential Oils		$82.1
Oilseed and Products		$508.3
TOTAL		$1,985.0

In addition, the U.S. imported an estimated $3.5 billion worth of newsprint.

SOURCE: *Agricultural Statistics 1980;* Department of Agriculture, Government Printing Office, Washington, D.C., 20402.

Table 2.—Estimates of Nonagricultural Imports—1978

Product	Value of Imports ($ Millions)
Synthetic Rubber	$148.9
Plastics	$517.5
Synthetic Fibers	$238.2
Pharmaceuticals	$292.3
Dyes, Tanning Agents	$170.7
Petro Waxes	$47.5
Coatings and Printing Inks	$40.0
Adhesives	$100.0
Detergents, Surfactants	$483.0
TOTAL	$2,038.1

SOURCE: Data sheets prepared by scientists at the USDA/ARS Northern Regional Laboratory at Peoria, Ill, for a Science and Education Aministration Task Force on Strategic and Essential Industrial Materials; March 1980. Data sources used varied and included issuances by the U.S. International Trade Commission and that collected by scientists from trade publications and firms. The study was intended to be illustrative rather than definitive.

NOTE: Agricultural imports figures for 1979 are 1.29 times the 1978 figures. The estimates of nonagricultural chemicals imported for 1979 are 1.15 times the 1978 figures. The trend in expenditures for agricultural imports, 1975-79, is mixed—essentials up 43 percent over the 5-year period, cocoa butter up 170 percent, drugs up 72 percent, and natural rubber up 127 percent, while expenditures for vegetable oils and waxes and for oilseeds remained about even. Expenditures for fibers other than cotton and jute declined during the period.

Discussion is limited to potential agricultural crops for which sufficient research indicates that their domestic production and use in the chemicals industry is chemically feasibile, agronomically possible, and economically viable. This paper, therefore, must be considered illustrative rather than definitive. Significantly more agronomic and economic research must be undertaken before definitive conclusions can be reached. At the same time, however, urgent public policy issues must be addressed promptly if our Nation is to have an assured supply of strategic and essential materials.

Importance to the United States

The United States imported an estimated $22.1 billion worth of agriculturally produced industrial materials and petroleum for feedstock during 1978; the figure for 1979 was slightly over $23 billion. The trend for the period 1975 through 1979 was an average annual increase of about 10 percent according to data in *Agricultural Statistics 1980* and estimates made in 1980 by Department of Agriculture researchers in industrial chemistry. The Nation could spend an additional $1.1 billion or more (1979 dollars) over the next 18 years acquiring and maintaining strategic stockpiles of natural rubber and castor oil (2).

In 1978, U.S. industry manufactured over 84.6 million metric tons (MT) of synthetic organic chemicals valued at about $754 per MT, for a total of about $63.8 billion (9). The manufacture of these chemicals consumed about 470 million barrels of petroleum, valued at about $15.1 billion, as feedstock (6). U.S. industry also purchased nearly $2 billion worth of agricultural imports including natural rubber, seed and vegetable oils and waxes, cocoa butter, fibers other than cotton or jute, drugs, and essential oils. In addition, the United States imported an estimated $3.5 billion worth of newsprint and other paper products and $2.05 billion worth of chemicals extracted from plants (about 50 percent) or made from petroleum (about 50 percent) (7).

Technologically, it is possible to produce domestically nearly all the aforementioned imported agricultural products and materials and to substitute domestically produced agricultural products for the 470 million barrels of imported petroleum feedstock. It is estimated that increased farming operations to produce these agricultural substitutes would consume an additional 200 million barrels of petroleum for fuel and agricultural chemicals; therefore, the net savings would be about 270 million barrels of imported oil per year.

Production of only one-third the annual domestic demand for strategic materials (natural rubber, castor oil, and sperm whale oil) would eliminate the need to stockpile them.

According to the Federal Emergency Management Agency, the national stockpiling requirement for natural rubber is about 800,000 MT. The stockpile contained about 100,000 MT in 1980, leaving a shortfall of about 700,000 MT. World production of natural rubber has been declining slightly and, on an annual basis, is only keeping pace with world demand. The annual demand of the United States, the largest single user of natural rubber, greatly influences the world supply-demand formula each year. Therefore, each time the United States attempts to purchase rubber for the strategic stockpile, the result is a dramatic increase in price. At the 1978-to-1982 average price for natural rubber ($1,287 per MT), acquisition of the rubber needed to meet the 800,000 MT stockpile requirement would cost the Federal Government about $900 million. Storage and management costs for this stockpile would run an estimated $7 million per year. Total costs, at constant 1982 dollars between now and the year 2000, would be slightly over $1 billion. If the United States domestically produced 270,000 MT of natural rubber per year, the need for stockpiling would not exist.

The stockpiling target for castor oil is about 9,981 MT. The present stockpile contains about 5,671 MT. Acquiring the 4,310 MT shortfall would cost an estimated $5.2 million. Acquiring and storing the material through the year 2000 would cost about $13.8 million (1979 dollars). Domestic production of one-third the annual U.S. demand (about 10,000 MT) would eliminate the stockpiling need.

Sperm oil is obtained from the sperm whale, an endangered species. Since U.S. law prohibits production or importation of sperm whale oil, the Nation has no stockpile of sperm whale oil. Alternatives are available and can be provided domestically.

Producing 100 percent of the strategic and essential industrial materials or their replacements would reduce U.S. foreign outlays by about $16.5 billion annually at constant 1979 dollars and demand levels. Savings for different levels of domestic production can also be calculated. In addition, domestic production of one-third the U.S. demand for these three strategic materials would save more than $1 billion of public money over the next 18 years (money that otherwise would be spent in acquiring and maintaining strategic stockpiles of natural rubber and castor oil) and would provide replacements for sperm whale oil. Such a program would increase demands for domestic agricultural production, thus transferring expenditures for foreign petroleum, chemical, and agricultural imports into expenditures for domestic agricultural products.

The United States has about 413 million acres of cropland and about 36 million acres of pasture and other land in farms that easily and inexpensively can be converted to crop production. This represents an immediately available crop production base of about 450 million acres (8). In 1979, America's farmers used 348 million acres for crop production: an uneconomically low use rate of about 77 percent. Production of substitutes for one-third to one-half the industrial materials purchased abroad would demand about 60 million acres of cropland. Production of food and fiber at the 1979 rates plus production of these materials would require 408 million acres of cropland: a utilization rate of nearly 91 percent. A problem would be the propensity for opportunists to produce commodities on fragile soils in years when prices are high and to abandon them in years of lower prices, leaving the State, Federal, or local government to pick up the costs of dealing with stream siltation, severe blowing of soils, encroachment of undesirable plant species, and other problems. A mechanism to prevent such practices, but achieve a 91 percent utilization rate of the U.S. cropland base, would have to be found.

The Nation has about 96 million additional acres of land that could be converted to crop production with more difficulty and expense than the 36 million acres cited above. Therefore, the Nation's total cropland base, or that land capable of sustained crop production under intensive cultivation by known methods, is 540 million acres. According to projections made by the Department of Agriculture (4), about 462 million acres of cropland will be needed in the year 2030 to meet domestic and foreign trade demands for food and fiber. This would leave 78 million acres of the cropland base to meet other production needs, assuming that this base is not converted to urban and other nonagricultural uses. Use of 462 million acres for food and fiber production and 60 million acres for industrial materials production would represent a 96.8 percent utilization rate of the Nation's cropland. At that rate of use, it might be possible to eliminate commodity support and subsidization programs for food and fiber.

Chemical Potential

It is technologically possible to provide domestic agricultural substitutes for nearly all the imported agriculturally produced industrial materials and a large share of the petroleum used as feedstock in the chemicals industry. The following table lists some of the potential domestic crops and what they might replace.

In addition to those plants identified in table 3, a number of others might be used to provide replacements for feedstocks in the chemicals industry. For example, research has already established that *Limnanthes, Lunaria, Valeriana, Cuphea*, and *Foeniculum* are potential sources of specific acids, esters, and oils used in industry. In addition, oils from existing agricultural crops such as soybeans, safflower, sunflower, linseed, corn, and other oilseed and vegetable oil crops could be used for certain industrial purposes.

Agronomic Potential

Development of the agricultural crops discussed herein could benefit nearly all of the Nation's agricultural areas. Guayule and jojoba, perennial arid-zone plants, can be produced in the arid Southwest. Crambe is a short- season annual crop which might be double-cropped in the major production areas of the Midwest, South, and Southeast. It would provide an alternative to corn or wheat in areas marginal for these crops. Kenaf, a dense-growing annual, is commercially valuable for making newsprint and other paper and fiber products. *Cuphea*, an annual, now is grown experimentally in Germany and the United States. It should adapt well to Northcentral, Northwest, Northeast, and Pacific Northwest United States. *Stokesia* could be produced in the Southeast, and *Vernonia* in the southern tier. Lesquerella could be grown in Central, Southcentral, and Southwestern United States, while *Limnanthes* is adapted to the Pacific Northwest. Both are annuals. *Lunaria* seems to be adapted to northern regions with long days and eventually might provide a crop for Alaska. Some

Table 3.—Potential Domestic Crops and Uses

Guayule	Hevea natural rubber, resins
Crambe	High erucic rape oil and petroleum feedstock
Jojoba	Sperm whale oil and imported waxes
Lesquerella	Castor oil
Vernonia - Stokesia	Epoxy oils
Kenaf	Imported newsprint and paper
Assorted oilseeds	Petrochemicals for coatings and other industrial products

SOURCE: L. H. Princen, *Alternate Industrial Feedstocks From Agriculture* (Peoria, Ill.: Northern Regional Research Center, Agricultural Research Service, U.S. Department of Agriculture, 1980).

Lunaria lines are biennial and some are annual. (The above paragraph is taken from Princen (3).)

Current Research

Current research on the above plants is extremely limited. A little genetics and agronomic work is being done. Less is being done on use of meals and other byproducts, including cellulose, left after extraction of the principal products. Guayule, jojoba, and crambe are being grown on semicommercial scale acreages. Limited plant breeding and agronomics research is under way for these three potential commodities. Some small-scale seed increase and agronomic work is under way with *Lunaria* and *Limnanthes* at universities in Oregon and Alaska. Limited commercialization work on jojoba is being done by the private sector and universities in the Southwest. Federal funding for research is greatest for guayule, a source of natural rubber, because of its importance to the military. However, the total 1981 expenditures committed to guayule research totaled only about $3 million. Research commitments to all other potential substitute commodities discussed herein were considerably less.

Research Needs

Little additional basic chemical research is needed for the commodities discussed in this paper. The next level of research would involve chemical engineering to develop efficient, economical extraction and processing systems, an area of proprietary interest in the private sector. Such research is needed, but if it is to be undertaken at public cost, arrangements will have to be made to sell, franchise, or license the processes for exclusive use by firms. Because of the present lack of risk capital in the private sector, public support of such research probably would be necessary if these plant materials are to be commercialized. However, current administration policy appears not to favor public sector support for agricultural research of this nature. In 1982, the Office of Management and Budget imposed rigid guidelines governing Federal research and directed the Department of Agriculture to terminate any ongoing research commercial in nature (1). Significantly, an article in *The Washington Post* during the week of November 8-12, 1982, noted that a White House report justified continued research on the space shuttle because of its commercial potential. It is interesting to note that the latest flight of the space shuttle, which the news media reported cost the government about $250 million, collected an estimated $38 million from private industry as fees for putting two satellites into orbit. If that is considered the commercial value of the flight, one may conclude that the other $212 million must be charged off to research and development, a subsidy to the private sector. Needed subsidies to develop agricultural materials substitutes would be modest by comparison.

The most needed research on these potential commodities in the immediate future is in the areas of plant breeding and agronomy. Byproduct use research also will be needed. It is not difficult to calculate the price at which plant oil extracts must be sold to compete with petroleum feedstocks in the chemicals industry, but the value of the meal and other byproducts are unknown because information on their possible uses is limited. This knowledge is vital to assessing commercialization potential. For instance, the late 1982 price of soybean oil was about 17.2 cents per pound, and the value of the meal was about 8.8 cents per pound. Total value of the processed commodity was about 26 cents per pound. At a price of $6 per bushel, soybeans sell for about 10 cents per pound off the farm. If there were no value in the meal, the farm price would have to be less to make processing the oil profitable. Such information is needed to assess the economic feasibility of commercialization. Enough work has been done on byproducts of commodities discussed in this paper to suggest that they may have values similar to those of byproducts from soybeans and other conventional oil crops.

Most of these new crop materials now being grown in research projects are from wild or nearly wild plants. Genetic improvements are needed to increase seed and oil yields and predictability of the plant under cultivation. In the absence of such genetic improvements in corn, average U.S. annual yields from unimproved stocks might be 8 to 10 bushels per acre, rather than the 109 obtained for 1979 from improved hybrids. While tenfold increases in crambe production are unrealistic, twofold increases are feasible. A threefold increase in seed yield and a 10-percent increase in oil yield, calculated from the average of present yields in different States, would produce 5,400 pounds of seeds, 2,700 pounds of oil, and 2,700 pounds of meals and other products per acre. Research is needed on how to cultivate the plant to obtain optimum yields of both seed and oil.

Little agronomic research has been done for potential new commodities other than crambe and guayule. Yield data from test plots reflect only initial efforts to cultivate plants using strains of seed that have not been genetically improved.

Economic Potential

Several factors must be integrated to estimate the economic benefits of using domestic production to replace agricultural imports and to substitute renewable agricultural materials for petroleum as feedstock in the chemicals industry.

Paramount is the question of the relative costs of substitutes and current sources of these materials. Next in importance is the degree of profitability in producing new agricultural raw material. The third major factor is the level of subsidization required by the agricultural industry to meet national strategic and essential materials needs.

The National Science Foundation and the Midwest Research Institute, in cooperation with universities in the Southwest and rubber companies, completed an exhaustive study of the commercial feasibility of establishing a domestic natural rubber industry based on guayule. According to that study, the price of imported rubber is expected to rise in the foreseeable future, particularly if world supplies continue to dwindle. The study estimates that the price for imported rubber and the costs of domestic production will converge in the late 1980's, making it equally as attractive economically to produce domestically as to import the material. The advantage of not having to import a strategic commodity over distant sea lanes in times of emergency is, of course, great.

Sperm whale oil is not legally available in the United States, and U.S. policy discourages foreign production; therefore, a substitute for this high-quality lubricant must be provided. Jojoba is an ideal substitute. Jojoba can also be a substitute for castor oil. Castor oil currently costs about 54.5 cents per pound. While castor oil has been produced in the United States, the bean contains toxic and allergenic properties that pose hazards for people and animals and problems for waste disposal. Its domestic production has, therefore, been discontinued. *Lesquerella* is another substitute for castor oil. Its cultivation poses no health hazard, and the meal can be processed for animal feed.

The primary economic consideration in substituting agricultural commodities for petroleum as feedstock in the chemicals industry is the price of petroleum. Currently, petroleum is imported at a price of about 10.6 cents per pound. In industrial uses, seed oils could sell at a higher price per pound than petroleum without increasing the price for the final chemicals produced. These plants yield chemicals in relatively pure form so that they can be used with little processing. Extraction of the same chemicals from petroleum is complex and expensive. The only true comparison of costs and feedstock values can be made when the value of the acids, esters, waxes, or other chemicals produced from the two different sources of feedstock are compared. This comparison cannot be made until semicommercial agronomic production is undertaken and engineering processes for extracting these new plant oils, at the prototype scale, are developed and tested. This will allow accounting for the total processing, agronomic production, and other costs to define total costs at the prototype and commercial scales of production.

Some cost projections can be made on the basis of available data. For example, initial attempts at production of crambe on semicommercial acreages in western Kentucky yielded 1,800 pounds of seed and 720 pounds of oil per acre. At the current price of petroleum (10.6 cents per pound), the oil from an acre of crambe would be worth $76. If one assumes that this oil is 25 percent more valuable as feedstock than petroleum because it requires less costly processing, its value would rise to $95 per acre. This compares favorably with the economic returns from wheat production of 30 bushels per acre in the same area. With even minimal increases in production, crambe might become an attractive substitute for current crops that are only marginally adapted to certain geographical areas. However, suppose research can triple the seed yield and increase oil content by 10 percent; then the crop would be valued at $286 per acre based on the current competitive price of imported petroleum. In addition, the meal can be fed to beef cattle. With a 25-percent value increase based on lower processing costs than petroleum, the value would rise to $357 per acre. Taking the average yield and mean price for corn in the United States during the past 5 years, corn for grain would be worth about $252 per acre. An assessment based on economics alone then might favor growing crambe over corn in that area.

During recent years, the Federal Government has spent between $7 billion and $14 billion annually to subsidize production of commodities that are already in surplus. If this subsidy were spent instead to encourage the domestic production of imported plant materials or to provide substitutes for petroleum feedstocks in the chemicals industry, the average subsidy on the 60 million acres would fall between $116 and $233 per acre per year.

Some estimates may also be made regarding the effects of a successful program to substitute domestic production for importation and agricultural commodities for petroleum feedstocks. If 60 million acres are used to produce such commodities, on-farm employment would increase by about 155,000 jobs, or about 7 percent over 1979 farm employment. The 60 million acres is equal to 133,333 average-sized farms, each employing 1.618 workers. If the assumption that one job in agriculturally related enterprises (transportation, processing, machinery and equipment, agricultural chemicals, sales, and management) will be created for each new onfarm job, the total job increase would be about 311,000. (In the combined agricultural and food industries, there were about 17 million workers in 1979, but only 2.7 million onfarm. This is a ratio of 6.2 to 1.) At average rates of use, these hypothetical 133,333 "new farms" would need 253,000 tractors; 173,000 trucks; about 120,000 harvesters of various kinds; and related equipment. Thus the benefits would spill over into the manufacturing sector. At average-use rates for all farms, production would consume about 2.9 million tons of fertilizers and about 200 million barrels of petroleum in addition to other products and services. (These figures were calculated from data contained in *Agricultural Statistics* 1980.)

Another consideration must be the impact on world demand and price for OPEC petroleum if the United States reduced its demand by nearly 740,000 barrels per day (270 million barrels per year). Evidence suggests that oil conservation efforts in the United States and other importing countries already have had major dampening effects on world production and pricing. This factor represents approximately 4 to 5 percent of our annual consumption of petroleum. However, should substitution of agricultural commodities drive down the price of oil, there would be incentive to switch back to petroleum as feedstock. Conversely, if the price of oil continued to rise, there would be incentives to switch back to agricultural substitutes.

In the event the world oil price decreased as the United States switched to agricultural alternatives, the United States would have increased leverage with suppliers as long as its option to substitute agricultural commodities were kept open. At this point, the issue would become a political rather than economic one.

Political Considerations

Political considerations underlying this issue revolve around two central questions: 1) what does the United States have to gain and lose in the international community, and 2) whose ox will get gored?

Exporting nations presumably would react unfavorably if the United States chooses to substitute domestic production for imported agricultural materials and petroleum. On the other hand, nations competing with the United States for these resources in the world market would be happy. Those who compete with the United States for marketing their food and fiber also would be happy. The complex effects of such a substitution strategy on any one nation are calculable but beyond the scope of this paper. Given that such effects can be calculated, the decision whether or not to substitute is as much political as it is economic.

On the domestic front, the key short-run issue for farmers, agricultural firms, and the Federal Government will be whether to subsidize production of new agricultural commodities instead of continuing to subsidize surplus production or support agreements to take land in surplus commodities out of production. As for defense, the issues are: 1) how much should we invest in stockpiling materials as opposed to encouraging domestic production of strategic materials to avoid stockpiling needs, and 2) what is it worth to have domestic control of strategic materials supplies?

Public policy discussion will be strongly affected by private sector concerns. Domestic production of these commodities will not be in the short-run interest of vertically integrated firms now producing chemicals from petroleum feedstock, or of those firms now importing and supplying such agricultural materials. However, the negative interest of these firms in the issue might be offset by the positive interest of industrial users of such intermediate chemicals and other products. For instance, the news publishers could be highly interested in shifting from imported newsprint and other paper to domestically produced paper, since current data suggest it can be produced domestically for less than the cost of importing it. It is possible that users of intermediate chemicals or finished products (coatings, paints, and printing inks) may encourage substitution if a superior or less costly product can be obtained in the long run, if the rate of price fluctuation is decreased, or if assurances of continued supply are increased. Consumers of the final products might be expected to support substitution if assurance of supply is increased, the rate of price fluctuation is decreased, and the general economy is benefited. This includes anyone who owns a house, paints an apartment, owns a car or household appliances, uses cosmetics, holds a job, purchases a toothbrush, or wears clothes made totally or partly of synthetic fibers. Military leaders might be expected to support domestic supply of strategic materials.

Policy Shifts Needed

Four domestic policy shifts are needed to facilitate any move toward domestic control and production of strategic and essential industrial materials. The first is from dependence on foreign nations for agriculturally based strategic materials to domestic supply of them. The $1.1 billion that would otherwise be spent acquiring and maintaining these stockpiles should be committed to this end.

The second shift is to a national policy of encouraging agricultural research that has foreseeable commercial application including participation with the private sector in commercialization activities, partly research and partly commercial in nature. Federally supported research should be able to take commercialization through the prototype or pilot scale of activity under conditions that assure private sector partners exclusive rights to use patentable processes or products for a period of time, thus allowing the firm to recapture its investments.

The third domestic policy change needed is to spend federal funds to support production of useful agricultural commodities rather than supporting production of surplus commodities or for paying farmers to discontinue production.

The fourth domestic policy change needed is to look at domestic production of agriculturally produced materials as a way of using our farm production potential rather than depending on foreign trade. The United States, along with most of its allies and friends, is competing for a limited foreign market with surplus commodities.

On the international scene, the government may have to be prepared to limit, initially, the import of petroleum to encourage U.S. firms to substitute domestically produced agricultural commodities. The reduced demand should provide increased leverage in negotiating prices for the remaining imports.

Conclusion

On the basis of "best case" assumptions, the chemical technology exists to substitute domestically produced renewable agricultural commodities for about 170 million barrels of petroleum annually and for about $6.3 billion worth of imported agriculturally produced materials. There is a potential to reduce expenditures by about $1.1 billion over the next 18 years for stockpiling natural rubber and castor oil and for providing a substitute for sperm whale oil. The possibility of finding a more constructive use for the dollars spent in maintaining our agricultural production capability also exists.

No further research on the basic chemistry of these materials is needed. What is needed now is research related to the agronomics of producing such commodities, plant breeding to improve seed and oil or fiber yields, and research into byproduct use. In tandem with these efforts, economic feasibility assessments and/or definition of the economic parameters for commercialization are needed.

Research or commercialization activities in partnership with private firms should be undertaken to develop prototype processing or other production facilities. Such commercialization activities must have an educational component. Industrial chemists are trained in the chemistry of using petroleum as feedstock. In the early development of the chemicals industry, plant materials and coal were used as feedstock. Farmers who might become involved in producing the plant materials for use in commercialization research will not know the best cultural practices.

It would not make sense for the United States to jump headlong into a substitution program, but sufficient resources should be committed to the kinds of activities suggested above to use or discard, with just cause, the many development options that exist.

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INFORMATION GATHERING AND DATA BASES THAT ARE PERTINENT TO THE DEVELOPMENT OF PLANT-DERIVED DRUGS

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Abstract

An important element of drug development using plants is the accumulation and analysis of pertinent research data and purported ethnomedical (folkloric) uses for plants. Due to the quantity of information frequently available in the literature and its appearance over many years from worldwide sources, this information is best stored and analyzed by computers. There are 10 automated data bases that provide data on plant sciences, agriculture, and the chemistry and pharmacology of natural products. One of these data bases, the Natural Products Alert (NAPRALERT) file, affords both bibliographic retrieval and textual and numeric data relevant to drug development,

Status of Interest in Drug Development From Plants

A careful analysis of the National Prescription Audit from 1952 through 1973 indicates that, contrary to general belief, the higher (flowering) plants continue to provide useful, if not essential, drugs for people of the United States and elsewhere (23). The National Prescription Audit (NPA) collects data on a monthly basis from a statistically significant number of community pharmacies throughout the United States. These data include the number of prescriptions dispensed, the trade mark or generic name of the product prescribed, and the price to the patient. Using these data and information on the origin of active principles (i.e., plant-derived, microbial metabolites, animal products, mineral and/or pure synthetic), it is possible to determine which of the thousands of different prescription items included in the NPA contain active principles extracted from higher plants.

From 1959-73, new and refilled prescriptions containing plant products represented 25 percent of all prescriptions dispensed from community pharmacies in the United States. Over the survey period, this percentage was never lower than 24 or higher than 26 percent in any year. Incomplete analysis of data for 1980 shows that plant-derived drugs still represent approximately 25 percent of the total prescriptions dispensed.

Since the total number and average price of prescriptions sold annually at community pharmacies are known, the value, at the consumer level, for those prescriptions containing active principles from higher plants can be calculated. However, it is difficult to make the same calculation on the increasing number of prescriptions and quantity of drugs dispensed from out- patient hospital pharmacies, extended care facilities, government hospitals, and other legitimate, but off-market, outlets because data from these sources are not conveniently available. Nevertheless, in consultation with academicians and others knowledgeable in pharmaceutical administration and economics, it was determined that U.S. noncommunity pharmacy prescription sales represent a dollar value almost equivalent to that of drugs dispensed from community pharmacies. According to NPA data, 1.532 billion new and refilled prescriptions were dispensed from community pharmacies in the United States in 1973. At an average cost to the consumer of $4.13 per prescription, the dollar value for the prescription market in 1973 was $6.327 billion. Since 25.2 percent of the prescriptions contained active principles of higher plant origin, the dollar cost to the consumer in 1973 was $1.594 billion. Adding almost an equal amount to this figure for plant-derived drugs dispensed from other outlets, an estimated total cost to the consumer was $3 billion in 1973.

Extrapolating from the 1959-73 data, and looking at high-volume prescription drugs dispensed from community pharmacies in 1980, the current annual cost to the consumer is estimated to be in excess of $8.116 billion.

NPA data for 1980 show that 41 species of higher plants yield all of the plant-derived prescription drugs. An additional 62 species of plants entered the prescription market in the form of crude extracts with active principles. Less than 50 pure compounds from plants were represented in the prescriptions analyzed. The pure compounds, the plants from which they are derived, and other plants used in extract form in prescriptions are listed in table 1.

Virtually all of the approximately 50 pure compounds used as prescription drugs (table 1) still are produced commercially by extraction of plant material or by chemical modification of extracted plant compounds. Although most of these drugs have

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*Presented at OTA workshop by N.R. Farnsworth.

Table 1.—Flowering Plants That Currently (1980) Are Sources of Useful Drug in the United States

Plant Names	Family	Type of Drug
Ammi majus	Umbelliferae	Xanthotoxin[a]
Ananas comosus	Bromeliaceae	Bromelain
Atropa belladonna	Solanaceae	Belladonna Extract
Avena sativa	Gramineae	Oatmeal Concentrate
Capsicum species (4)	Solanaceae	Capsicum Oleoresin
Carica papaya	Caricaceae	Papain
Cassia acutifolia	Leguminosae	Sennosides A + B
Cassia angustifolia	Leguminosae	Sennosides A + B
Catharanthus roseus	Apocynaceae	Leurocristine (vincristine)
		Vincaleukoblastine (vinblastine)
Cinchona species (3)	Rubiaceae	Quinine
		Quinine
Citrus limon	Rutaceae	Pectin
Colchicum autumnale	Liliacae	Colchicine
Digitalis lanata	Scrophulariaceae	Digoxin
		Lanatoside C
		Acetyligitoxin
Digitalis purpurea	Scrophulariaceae	Digitoxin
		Digitalis whole leaf
Dioscorea species (several)	Dioscoreaceae	Diosgenin
Duboisia myoporoides	Solanaceae	Atropine
		Hyoscyamine
		Scopolamine
Ephedra sinica	Ephedraceae	*Ephedrine
		*Pseudoephedrine
Glycine max	Leguminosae	Sitosterols
Papaver somniferum	Papaveraceae	Opium
		Codeine
		Morphine
		Noscapine
		*Papaverine
Physostigma venenosum	Leguminosae	Physostigmine (Eserine)
Pilocarpus jaborandi	Rutaceae	Pilocarpine
Plantago species (3)	Plantaginaceae	Psyllium husks
Podophyllum peltatum	Berberidaceae	Podophyllin
Prunus domestica	Rosaceae	Prune Concentrate
Rauvolfia serpentina	Apocynaceae	Reserpine
		Alseroxylon Fraction
		Powdered whole root Rauwolfia
Rauvolfia vomitoria	Apocynaceae	Deserpidine
		Reserpine
		Rescinnamine
Rhamnus purshiana	Rhamnacee	Cascara Bark
		Casanthranol
Rheum species (4)	Polygonaceae	Rhubarb Root
Ricinus communis	Euphorbiaceae	Castor Oil
		Ricinoleic Acid
Veratrum viride	Liliaceae	Veratrum viride Extract
		Cryptennamine

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[a] Underlined names indicate single chemical compounds of known structure.

*Also produced by synthesis

been synthesized, synthesis is not commercially feasible, with the exception of a few drugs such as ephedrine, pseudoephedrine, and papaverine.

In addition to the prescription drugs, the sale of herbal teas in the United States is estimated at least $200 million annually and the sale of over-the-counter (OTC) drugs obtained from plants is probably over $1 billion. For example, about one-half of the OTC laxative preparations sold annually in the United States are of plant origin. In 1980, exclusive of prescription sales, the laxative market was about $331 million (an increase of 10.3 percent over 1979). Data such as these are unavailable from other countries, but a similar incidence of use is likely in most of the developed countries.

One might presume that with a current market value at the consumer level in excess of $8 billion annually in the United States, most pharmaceutical firms would have major research programs designed to discover new drugs from plants. This is not the case. In 1974 the American pharmaceutical industry's total R&D budget for pharmaceuticals for human use was $722.7 million. Only one firm was involved in direct research to explore plants for new drugs. At that time a conservative estimate suggests that the annual research budget for that single program was less than $150,000. Although much has been written in scientific journals of this country and abroad that should spark industrial interest to invest in this area of research,* interest in this country has declined. Today there are no U.S. pharmaceutical manufacturers involved in a research program designed to discover new drugs from higher plants.

Other developed countries generally have followed the United States pattern, with two major exceptions: West Germany and Japan. Exploration for new plant-derived drugs in West Germany, however, has not captured the imagination of large pharmaceutical firms. Instead, these studies are supported by many small pharmaceutical manufacturers.

The Japanese situation is nothing short of phenomenal. Not only do Japanese academicians receive government and industrial support for research on plant drugs, but Japanese pharmaceutical firms also have major research departments dedicated to the same goal. Scientific papers from Japanese research laboratories relating to drug-plant development generally are of high quality and outnumber those from the United States by at least tenfold. In addition, Japanese patents for plant-derived biologically active substances outnumber those from the United States by a factor of at least 50.

Factors Responsible for Decline of Interest in Drug Plant Discovery

Important decisionmakers connected with drug development apparently are unaware of the extent to which plants contribute to our source of drugs. During the past three or four decades, research administrators have been scientists trained and experienced primarily in synthetic organic chemistry, biochemistry, molecular biology, microbiology, medicine, or related fields. Plant sciences have not had a voice in corporate or high-level governmental decisionmaking, except in the area of basic agriculture. Further, science has advanced to a point where interest has not been on the intact organism—whether it be plant, animal, or microbe—but rather on the cell, cell contents, and cell biochemistry. Typical industrial drug development increasingly has involved synthesis of molecules based on structure-activity relationships, and natural product drug development has been restricted to antibiotic production by micro-organisms.

If drug development programs now are based on synthesis and involve structure-activity relationships, what scientific process is available to identify plant-derived drugs? Most useful drugs derived from higher plants have been "discovered" through scientific inquiry into alleged folkloric claims of therapeutic effects. The only other approach used in recent years, although unsuccessful, has been the random collection of plants followed by pharmacologic evaluation. This approach has been modified in several ways. For example, the Smith, Kline and French Pharmaceutical Co. (SKF) had an extensive program for several years. SKF sent workers into the field to carry out "spot tests" for alkaloids on any plant that was reasonably abundant. Plants giving positive tests were collected in 1- to 5-kg amounts and sent to the parent research laboratories in Philadelphia. The total alkaloid fraction was separated from each species and then subjected to a series of pharmacological tests. Nothing has ever been published to provide an understanding of the rationale for the selection of pharmacological "screens" used in this program. The total number of plants bioassayed was also unreported, although they probably numbered several hundred species. Many scientific reports came out of the SKF studies, but they lacked pharmacologic information.

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*If none have been tested in humans yet.

A major program of the National Cancer Institute involving the "screening" of plants randomly collected worldwide ended in late 1981. This program, which was started in about 1956, tested some 35,000 species of plants for antitumor activity in laboratory animals. Although a large number of highly active antitumor agents were discovered by the NCI program, none have been approved for use against human cancer by the Food and Drug Administration (FDA). A few remain to be studied in humans. These* plant-derived antitumor agents that appear promising and presumably will undergo eventual testing in humans are tripdiolide, indicine-N-oxide, baccharin, isobaccharin, taxol, 10B-hydroxy with anolide, bruceantin, and homoharringtonine. The results of this program have been reviewed through early 1982 (8,12,60,61).

One could argue that this approach of "blind" screening any and all plants available in sufficient quantity for testing is entirely unscientific and too costly to be continued. Perhaps these are reasons for the NCI's cancelling its program on antitumor plants. Surely a program that fails to produce a useful drug after 25 years of testing more than 35,000 species of plants must be examined to determine what went wrong!

Speaking in defense of the NCI screening program, Suffness and Douros (59) stated:

> It is unfortunate that there has been a mutual skepticism between theoretical researchers, who are interested in a "rational" approach of discovering the biological differences between neoplastic and normal cells in order to develop drugs, and the approach of the empiricists, with the former group feeling that the latter are using a hit or miss unscientific approach and the latter feeling the former are divorced from the practical aspects of the problems. One hopes that this situation will progress in such a way that the information gained by the empiricists can be used to help the theorists develop new experimental methodologies and that the theoretical information produced by the rationalists can help the empiricists in their research. Structural analysis of new compounds developed through an empirical approach has given us the basis to develop analogs of a compound which might be beneficial and better than the parent active compound.

With the amount of data now available from the NCI antitumor plant program, it would be interesting and useful to conduct a scientific retrospective analysis on data of all 35,000 species of plants tested in this program.

A program at the Eli Lilly Co.* discovered two useful antitumor drugs that still are widely used today. This program identified about 440 species of plants for inclusion in a broad biological screening program, based on literature reports and recommendations of Dr. Gordon Svoboda. *Catharanthyus roseus*, the Madagascar periwinkle, was the 40th species bioassayed within the program and yielded the useful antitumor agents leurocristine and vincaleukoblastine. From the discovery of the antitumor activity of a crude extract of this plant, through the isolation, biological testing, toxicity, and clinical trials of vincaleukoblastine, less than 4 years were required for FDA approval and the marketing of this drug for the treatment of human cancer. The second useful alkaloid, leurocristine, was marketed 2 years later.

Nothwithstanding the work on *Catharanthus*, industry's development of useful drugs from higher plants during the past 30 years has not been more productive than government efforts. Since 1950, pharmaceutical companies have produced only three plant-derived drugs that have reached the U.S. prescription market: reserpine (and the related deserpidine and rescinnamine), vincaleukoblastine, and leurocristine. The total number of industry research dollars required to discover these drugs has been miniscule compared with the cost of placing synthetic drugs on the market. If industry invests next to nothing in drug-plant development, what can it expect in the way of marketable compounds?

Perhaps a major deterrent to industrial interest in plant drug development is that much of the unexplored flora of the world currently is found in tropical and/or semitropical areas, especially in developing countries. Because many of the countries' governments are considered to be unstable, an uninterrupted supply of raw material for manufacture of a new drug developed from a plant indigenous to such areas may not always be assured. This seems a weak argument to justify the lack of plant drug development, since rarely is a plant found only in one country. In addition, alternate sources of supply, including cultivation, always should be developed when a useful drug is discovered.

Some companies feel that patent protection is less secure with natural products than with synthetics. We have not been able to document examples supporting this contention. To the contrary, there is no evidence that the Eli Lilly Co. experienced difficulties with patents assigned to them for the antitumor alkaloids vinceleukoblastine and leurocristine, whose annual worldwide sales are $50 million at the manufacturer's level.

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*(5), (11), (14), (15), (16), (17), (18), (19), (20), (23), (24), (54), (55).

*See paper by Svoboda in this volume.

Information That Should Be Included in Data Base Useful for Drug Development From Plants

A data base that would be useful in a program of drug development from plants should include the following information:

The Plant

Information on the plant should include: its most current Latin binomial and all recently employed botanical synonyms, along with the authority, varieties, subspecies and lower taxonomic groups, the family name of the plant, and vernacular (common) names; the geographic area where the plant was collected and all known areas where the plant occurs naturally or under cultivation; whether or not a voucher specimen representing the investigated material was prepared and stored; and the part(s) of the plant studied.

Ethnomedical Uses

Documentation of the crude plant material (fresh, dried, pulverized) or type of extract employed in preparing the ethnomedical dosage form, route of administration, dose employed, dosage regimen, side effects, and beneficial effects claimed should be retrievable from the data base. The ethnomedical claim(s) should also be computerized to allow for retrieval of information on analysis of related effects. For example, a plant extract may be alleged to be useful as an ethnomedical preparation for arthritis and/or rheumatism. Experimental data may have been reported elsewhere indicating that an extract of the same plant has shown anti-inflammatory activity in vivo and in vitro. It may also have been reported to have analgesic activity and to inhibit prostaglandin synthetase in vitro. These experimental pharmacologic effects suggest that the extract could be beneficial in treating arthritis and/or rheumatism. Ideally, a data base useful for drug development would have the capability of relating general ethnomedical information with experimental data to predict useful drug effects.

Chemical Constituents of Plants

It is important to be able to retrieve data on the chemical constituents of plants, the part of the plant in which the constituent is reported to be present, the range of percentage yield of the chemical, and any available data on seasonal or other variations in chemical quality or quantity.

If a chemical compound is known to produce a pharmacologic effect, the presence of such a compound in the plant may explain either the experimental pharmacology of an extract of the plant or an ethnomedical claim relating to the effect of the known chemical constituent. An appropriate computer analysis relating ethnomedical claims, experimental pharmacology of plant extracts, occurrence of chemical constituents, and pharmacological effects of naturally occurring chemical constituents may indicate that all aspects of a given problem have been studied, even though the answer is scattered in several publications from different parts of the world. Such computer analysis can prevent costly and time-consuming redundant research. Sources of all data should be coded and specifically linked for subsequent retrieval and reevaluation or reinterpretation as may be necessary.

Additional valuable information in a data base is classification of various naturally occurring chemical compounds by general class, sub-structure, and functional groups on the molecule. Computer analysis of a series of plant-derived chemical constituents with regard to chemical structure biological effects could be useful in the advanced stages of drug development.

Experimental Biological Testing

For Plant Extracts. It is important to be able to identify the type of solvent used to prepare an extract of a plant tested for biological activity, since, for example, an extract using petroleum ether would be expected to react differently than one prepared with ethanol. Further, the type of biological test—i.e., in vitro, in vivo, or human study—is important, since the credibility of data with respect to its ultimate value as a drug would be of the order in vitro < in vivo < human study.

A system for identifying similar and related biological effects would be required if computer analysis of the data is anticipated. Thus, central nervous system, autonomic, hematologic, chemotherapeutic, and/or hormonal effects, etc. should be organized so they can be retrieved and analyzed as a group or for a specific effect within each group. Test species should be identifiable, since data using rodents, for example, may not be as significant as data derived from primate studies. The route of administration is important, as is the dose, dosing scheduled, and qualitative and/or quantitative result. The disease states of animal models or the type of experimental model also should be documented.

For Pure Compounds. All of the above parameters should be documented for test results on plant chemical constituents, with the obvious exception that the type extract would not apply.

Other Important Information

It would be of interest in any plant-derived drug development program to be able to retrieve references to naturally occurring chemical compounds that have been partially or completely synthesized. Similarly, data relating studies on the cultivation of useful drug plants and the effects of cultivation conditions, processing, and storage on the yield of useful active constituents would be useful in a data base for drug-development purposes.

Eventually plant-derived drugs probably will be produced by cell culture, although the necessary technology is not so advanced that commercial applications of tissue culture for this purpose will be available soon. Little work is being supported either by industry or government in the United States to develop plant tissue culture for this practical application.

Similarly, genetic engineering some day may be applied to producing plant-derived drugs. However, the production of useful drugs by plants is always a multistage process. Transfer of several sets of genes to microbes would be required to produce secondary metabolites that are useful drugs. We do not know of any current efforts in this area. Most likely a detailed examination of the biosynthesis of the drug that would be a candidate for production by genetic engineering would have to be carried out in each case. Again, basic studies that would provide this type of information are not being supported to any extent in this country.

Accessibility of Data Pertinent to Plant-Derived Development

Data of value in organizing and implementing an effective plant-derived drug development program are difficult to obtain through currently available on-line data bases. Further, much of the useful pharmacologic data on plant extracts was published prior to the earliest data covered by all of the available online data bases. Also, the format in which data can be retrieved from most available systems is inadequate for practical use in a major program.

It has been our experience that the pharmaceutical companies are reluctant to share data derived from testing plant extracts, even if the data are negative and are of no commercial interest to the firms. In the United States alone, some pharmacological data on perhaps several thousand species of plants have been documented by industrial firms, but remain unpublished. Negative data are as important as positive data in a broad plant-based drug development program, and it is unfortunate that some mechanism cannot be found to persuade industrial firms to make their unpublished in-house pharmacologic data on plants available to the general scientific community.

The National Cancer Institute published negative data regularly at the beginning of the plant screening program. This apparently became an expensive exercise because most of the data now remain unpublished. If one requests information on a few species of plants, NCI will provide the information from its files, but probably would not supply large amounts of data.

If one examines the format for the initial negative data published by NCI on testing plants for antitumor activity, it is obvious that much of the space-consuming information was superfluous—i.e., one line of data for each dose level tested. Since all the data are computerized, NCI should be encouraged to produce several volumes of negative data, allowing only one line per species with similar testing conditions. An entry of data would then appear as follows: **Genus-Species-Authority-Family-Country Where Collected-Part-Tumor System.** Such a list of negative data would be of enormous interest to scientists throughout the world and would help them in selecting new plants for study without duplicating past work.

A similar problem exists with obtaining large amounts of useful data from published reports. For example, there are several hundred literature reports in which large numbers of plants have been screened for one to at least thirty biological effects. The names of plants in these multiple-entry reports rarely are obtainable from the subject indices of *Chemical Abstracts or Biological Abstracts,* and presumably from data bases using these sources.

Steps Involved in Gathering Information and Implementing a Plant Drug Development Progam

Diczfalusy (11) has discussed the general steps in developing drugs of plant origin. After the initial decision is made concerning how candidate plants are to be selected for investigation, procedures to be followed are reasonably straightforward (see table 2).

Information Gathering

Suffness and Douros (59) have given their views on the relative advantages of using folkloric information, botanical relationship, and random collection approaches to identifying plants for inclusion in the NCI screening program (see table 3). If the plants to be screened are not chosen randomly, they should be chosen on the basis of available information.

Information-gathering to identify candidate plants for study will vary considerably, but most likely will necessitate searching for data in the following areas.

Ethnomedical data. Ethnomedical (folkloric) information on plants is not indexed or abstracted in any organized way. Sources include books on medical botany, review articles, floras of various geographic areas, pharmacopoeias of different countries, anthropological writings, folkloric writings, and popular books on uses of plants. No one can be reasonably certain that all data collected for a given plant or for a biological effect of interest have been acquired from ethnomedical reports. To the best of our knowledge, only the USDA data base* and our NAPRALERT system (to be described sub-

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*See paper by Duke in this volume.

Table 2.—Selection of Approachs for Drug Development From Plants[a]

	Method of Selection	Advantages	Disadvantages
1.	Folklore Use	High ratio of activity Lower screening costs	Role of psychology in folk medicine Secrecy of primitive cultures Difficulty of botanical identification Use of complex plant mixtures Use of rare plants High procurement costs Leads may be missed Limited amount of screening possible Lack of novel active compounds
2.	Botanical Relationship	High ratio of activity and Discovery of useful analogs	Reisolation of known compounds
3.	Random Collection	Best chance to find novel active compounds Plants are more readily available	Low percentage of active leads Large bioassay capacity needed High cost per lead

[a] Modified from Suffness and Douros (1979).

Table 3.—Steps Required for Drug Development From Plants

1. Decision on method to select plants
2. Preparation of extracts for bioassay.
3. Initial collection and identification of plants
4. Bioassay of plants
5. Recollection of active plants for confirmation of activity
6. Fractionation of active plants following bioassay.
7. Isolation of active compound(s) in sufficient quantity for bioassay and identification or structure elucidation
8. Determination of pharmacologic profile for active compound(s)
9. Acute and chronic toxicity studies
10. Large scale preparation of the active compound(s)
    a. Large scale procurement of active plant
    b. Pilot plant scale development of efficient isolation procedures
11. Initiate studies designed to prepare the active compound by complete synthesis and to prepare active analogs
12. Formulation studies
13. Pharmacokinetic and metabolism studies
14. File an Investigational New Drug Application (INDA) with the Food and Drug Administration
15. Phase I human studies
16. Phase II human studies
17. Phase III-IV human studies
18. File a New Drug Application (NDA) with the Food and Drug Administration
19. Market the new drug

sequently) contain retrievable ethnomedical information. Some people discount the value of folkloric reports of medical efficacy of plants, but in doing so refute the historical documentation of how such information was used in the discovery of such major drugs as digitoxin, reserpine, tubocurarine quinine, codeine, morphine, and others. The degree to which one uses ethnomedical information will vary according to the background, training, and capabilities of scientists involved in a drug-development program.

Experimental Data on Plants. The subject indices of several abstracting services usually identify plants tested for biological effects or plants from which chemical compounds have been obtained. We routinely use those abstracting services listed in table 4, which identify the period and type of literature covered in each case.

A word of caution has to be given, however. We have found less information on plants in decennial indices of **Chemical Abstracts** when compared to annual indices. We have also found that a great deal

Table 4.—Secondary Literature Indices Used in the NAPRALERT Program

Title	Period Covered
INDEX CATALOG OF THE SURGEON GENERAL	1880 - 1961
INDEX MEDICUS	1897 - 1927; 1960 to present
CHEMICAL ABSTRACTS	1907 to present
QUARTERLY CUMULATIVE INDEX MEDICUS	1916 - 1956
BIOLOGICAL ABSTRACTS	1926 to present
CURRENT LIST OF MEDICAL LITERATURE	1941 - 1959
UNITED STATES ARMED FORCES MEDICAL JOURNAL	1950 - 1960
NATIONAL LIBRARY OF MEDICINE CATALOG	1956 - 1965
NATIONAL LIBRARY OF MEDICINE CURRENT CATALOG, CUMULATIVE LISTING	1966 to present
CURRENT CONTENTS, LIFE SCIENCES	1967 to present

of useful information, especially concerning pharmacological effects of plant extracts, is found in earlier abstracting services (i.e., those indicated in table 4 that cover periods prior to 1907). We also routinely check the bibliographies of pertinent articles, especially review articles, on subjects of concern to the area of the chemistry and pharmacology of specific plants and/or specific pharmacologic effects and find a significant number of useful papers that were not identified through systematic literature searches of the services indicated in table 4.

If current work indicates that one or more research groups throughout the world are publishing extensively in an area of interest, correspondence with those groups usually uncovers additional literature that is not usually available through indexing services.

Finally, the use of one or more of the online computer data bases to acquire citations and/or abstracts on a particular subject may be advisable.

In our laboratory, experimental work on a plant does not commence until we have acquired all of the ethnomedical and scientific literature available through the aforementioned means, including data on taxa closely related to the plant of interest.

Plant Collection. It has been our experience that although botanists are essential to the success of plant-derived drug development programs, they are the most unappreciated of the scientists involved in such a program. The botanist can not only clarify nomenclatural problems but has the credentials to contact other botanists in countries where the plants of interest grow. The botanist can provide sources of background information that would be unknown to the chemist and/or pharmacologist. Often this information is critical to a project's success. Through field work, the botanist can clarify vague points found in the literature on which several varieties of a species should be collected and can gather additional information from users of plants in the area where collections are to be made. These data may be useful to the pharmacologist on a drug development team in designing an animal study to assess the biological effects of a plant.

A number of government regulations pertaining to plant importation must be considered. For example, depending on the method used, fumigation of a plant entering the United States could produce chemical changes in the plant, rendering the chemical constituents inactive. The botanist can maintain communication with government botanists at points where plants enter the country and often can prevent such problems.

Bioassay Procedures. A critical stage in drug development from plants is the selection and implementation of bioassay procedures and interpretation of their results. Few pharmacologists are experienced in evaluating crude plant extracts or are interested in developing bioassay systems outside their own area of interest. In a large program, where several pharmacologists can become involved, "specialization" may be possible. However, even though a program is designed to identify only one or two types of biological activity, it would be cost ineffective not to carry out as many bioassays as possible, since the expense of acquiring the plant may be quite high.

Because there is inherent variation in laboratory animal experimentation, drug development programs involving plants should include a series of so-called in vitro "pre-screens." Plants should be selected on the basis of having predictive activity in animals and/or humans. Examples of some in vitro bioassays used for plant extracts are presented in table 5. If initial in vitro activity seems promising, in vivo activity can be confirmed in laboratory animals. Alternatively, isolation of the compound responsible for the activity can be accomplished using bioassay-directed fractionation with simple, rapid, and less expensive in vitro tests. The pure compound then can be tested in laboratory animals.

Many ubiquitous chemical compounds found in plants elicit biological effects but have no practical use as drugs. It would be important to identify such compounds, carry out a simple chemical test to indicate the presence of the compound in plants to be bioassayed, then modify experiments to rule out the effect of the undesired ubiquitous compound.

Isolation and Identification of Biologically Active Principles From Plants. Presuming that the goal of a drug development program is to develop pharmaceuticals, it is first necessary to establish a biological effect for a plant, then isolate the compound(s) responsible for the effect by bioassay-directed fractionation. Some biological activity may not be detected by means of a simple and rapid in vitro bioassay, thus presenting a major problem. If, however, the desired biological activity can be demonstrated in a laboratory animal after one or two doses, the in vivo bioassay can be used as an aid to fractionation. It is most useful to have bioassay capability in-house rather than to rely on outside chemical work.

Routine techniques are available for isolation and purification of the active principle(s) after one has fractionated a plant so that biological activity has been enriched severalfold. Column chromatography, ion-exchange, droplet counter-current chromatography, and high performance liquid chromatography are some well-established techniques. However, if the active compound is to be developed into a marketable item, a practical means for isolating it from the plant must be found. Few compounds exist that could be separated economically from plants by chromatographic techniques and every effort should be made to use simplified procedures.

Once the active principle has been obtained in pure form, identification is routine if it is a known substance. In cases of novel compounds, methods are available to determine the structures in a relatively short period of time, providing that modern instrumentation is available, including pmr, cmr, ms, and X-ray crystallography equipment.

Clinical Evaluation and Marketing. Any drug development program, whether it is industrial, academic, or governmental, must at some period involve the partnership of an industrial firm. Academia and Government usually do not have the capability to market a drug, but industry has the experience and know-how. Clinical evaluation is an expensive and complicated process, and is possible in the United States only after filing an Investigational New Drug Application (INDA) with the Food and Drug Administration (FDA). If approved, human experimentation within certain guidelines is allowed. Prior to marketing a drug, a New Drug Application (NDA) must be filed with FDA, providing all data from the results of Phase I-IV human studies allowed by the INDA. The drug, if approved, may then be marketed. The estimated cost for developing a drug varies depending on the clinical applications, but would not be less than $5 million and could be as high as $35 million per new drug.

Data Bases Pertinent to Drug Plant Development

There are about 1,000 online data bases—i.e., those searchable by the user from various types of terminals (10,27,66). Ten data bases seem to have information useful to a plant-derived drug develop-

Table 5.—Examples of in vitro Bioassays That Are Predictive for Useful Drug Effects or Improvement of Health

Type Assay	Type System	Implied Useful Effect	Reference
Adenosine deaminase inhibition	in vitro	Enhancement of drug efficacy	Kalckar, 1947
Angiotensin-converting enzyme inhibition	in vitro	Antihypertensive	Yun, Chung & Han, 1981
Antibacterial activity	bacterial culture	Antiinfective	Farnsworth, et al., 1966 Mitscher, et al., 1972
Antifungal activity	fungal culture	Antiinfective	Farnsworth, et al., 1966 Mitscher, et al., 1972
Antimitotic activity	cell culture	Anticancer	Suffness & Douros, 1982 Abbott, 1980 bade, et al., 1981
Antimutagenic activity	cell culture or bacterial culture	Anticancer	Calle & Sullivan, 1982 Katak, et al., 1980 Stich, Rosen & Bryson, 1982 Wood, et al., 1982
Antiviral	cell culture	Antiinfective, anticancer	Farnsworth, et al., 1966 Markkanen, et al., 1981
ATPase inhibition	in vitro	Cardiotonic	Barnett, 1970; Chen, et al., 1982 Duggan & Noll, 1965
Benzpyrene hydroxylase (AHH) inhibition	in vitro	Carcinogenesis inhibition	Pezzuto, et al., 1978
Cell transformation	cell culture	Carcinogenicity detection	Merriman & Bertram, 1979 Nescow & Heidelberger, 1976
Cytotoxicity	cell culture	Anticancer	Suffness & Douros, 1982 Geran, et al.,
Free radicals	in vitro; cell culture	Anticancer	Sarriff, White & DiVito, 1979 Tappel, 1972
HMG-CoA reductase inhibition[a]	in vitro	Antihypercholesterolemic, antiatherosclerotic	Stacpoole, Varnado & Island, 1982
Human stem cell assay	cell culture	Anticancer	Salmon, et al., 1978 VonHoff, et al., 1981

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[a] β-Hydroxy-β-methylglutaryl CoA reductase

Type Assay	Type System	Implied Useful Effect	Reference
Insect antifeedant	*in vitro*	Prevent crop damage and insect-borne diseases	Meisner, *et al.*, 1981 Munakata & Wada, 1981
Insecticide	*in vitro*	Prevent crop damage and insect-borne diseases	Su, Horvat & Jilani, 1982 Jacobson, *et al.*, 1950
Molluscicide	*in vitro*	Lower incidence of snail-borne diseases, i.e. schistosomiasis	Anon., 1965
Monoamine oxidase (MAO) inhibition	*in vitro*	Antihypertensive	Robinson, *et al.*, 1968
Mutagenicity	cell culture or bacterial culture	Carcinogenicity detection	Ames, McCann & Yamasaki, 1975 O'Neill, *et al.*, 1977 Ungsurungsie, *et al.*, 1982 Pezzuto, Moore & Hecht, 1981
Nucleic acid biosynthesis	*in vitro*; cell culture	Antibiotic	Robinson, *et al.*, 1968 Kuchler, 1977
Phosphodiesterase inhibition	*in vitro*	Anticancer	Nikaido, *et al.*, 1981
Piscicide activity	*in vitro*	Predictive for molluscicide effect	Bade, *et al.*, 1981
Platelet aggregation inhibition	*in vitro*	Cardiovascular problems	Makheja, Vanderhoek & Bailey, 1979
Prostaglandin synthetase inhibition	*in vitro*	Antiinflammatory	Ohuchi, *et al.*, 1981 Saeed, *et al.*, 1981
Protease inhibition	*in vitro*	Anticancer; plant protection	Lewasz, Rys & Reda, 1981 Norioka, Omichi & Ikenaka, 1982 Ohkoshi, 1981
Protein biosynthesis	*in vitro*; cell culture	Antibiotic; anticancer	Pezzuto & Hecht, 1980 Woodward, Ivey & Herbert, 1974
Sister chromatid exchange	cell culture	Carcinogenicity detection	Perry & Evans, 1975
Tyrosine hydroxylase inhibition	*in vitro*	Antihypertensive	Waymire, Bjur & Weiner, 1971
Unscheduled DNA synthesis	cell culture	Carcinogenicity detection	Freedman & San, 1980 Sirica, *et al.*, 1980

ment program. Nine of these are summarized in table 6, the tenth is developed at the USDA by Dr. James Duke.* We are unaware of data bases that contain information pertinent to plant-derived drug development in the People's Republic of China, Japan, or the U.S.S.R.

AGRICOLA (formerly CAIN). This database is produced by USDA but is available through commercial vendors such as BRS, DIALOG, and others. It covers the literature from 1970 to the present on agricultural chemistry and engineering, food and plant science, nutrition, and related agricultural fields. Approximately 6,500 journals are reviewed for input. The bibliographic file is composed of 90 percent journal articles and 10 percent monographs, published proceedings, and/or theses. Subject analysis by the user is carried out using controlled keywords—i.e., those provided in a prepared thesaurus or through enriched titles. Chemical identifiers include the use of nomenclature codes, fragmentation schemes, or the chemical name as it appears in the source of data.

BIOSIS PREVIEWS. This file has been produced by Biosciences Information Services and is also available through commercial vendors. Its subject matter includes life science data for microbiology, the plant and animal sciences, experimental medicine, agriculture, pharmacology, ecology, biochemistry, and biophysics. A search of the file provides bibliographic data for information obtained from approximately 94 percent journal articles, less than 1 percent government documents, and the remainder from monographs, published proceedings, or theses. Search methods include the use of enriched titles, uncontrolled keywords (i.e., keywords selected by the user and not from a prepared thesaurus), and subject headings that may appear in the title. Chemical identification uses the same type information described above (see AGRICOLA).

CAB SYSTEM. The Commonwealth Agricultural Bureau System of England produces this file, which is also available in the United States. The CAB System has bibliographic data and abstracts obtained from a review of approximately 8,000 journal titles covering the literature from 1973 on. It represents a compilation of 20 agricultural science databases, and includes subjects such as animal and plant breeding abstracts, plant pathology, nutrition, entomology, and related fields. Searching this database requires the use of uncontrolled keywords and subject titles.

FSTA. This is an acronym for Food Sciences and Technology Abstracts. Its subjects include agricultural chemistry and engineering, food science, home economics, and patents from approximately 1,300 journal titles. The resulting database is composed of 85 percent journal articles, 10 percent patent information, and 5 percent monograph, government document, or theses data. Search techniques use uncontrolled keywords and/or enriched titles. Chemical compounds again are identified using registry codes, fragmentation schemes, or the name which appears in the document processed. All data are bibliographic with abstract summaries for the years 1969 to the present.

CACON (Chemical Abstracts Condensate). CACON is one of the largest and most widely distributed bibliographic databases in the world. This file is a product of Chemical Abstract Services and covers most life sciences and physical sciences from 1968 on. Literature coverage includes input from approximately 14,000 journal titles and results in a computerized file made up of 72 percent journal articles; 2 percent government documents; 10 percent monographs, published proceedings, or theses; and 16 percent patent information. Subject retrieval is carried out using uncontrolled keywords, which may appear in the article title or its abstract, subject headings, and/or word strings. The latter are searched in the computerized abstract material.

MEDLINE. This file, produced by the National Library of Medicine (NLM), covers the literature from 1974 on. Depending on the literature period of interest, it is offered either on-line or off-line. Input data are obtained from approximately 3,000 journals titles comprising life sciences and/or medical information. These data are represented in the file by 99 percent journal articles, of which 65 percent are in the English language. The remaining 1 percent of data represents government documents. Retrieval provides bibliographic data with an abstract summary and is obtained by using keywords and/or subject headings.

IMEPLAM. This is the acronym for Instituto Mexicano Para el Estudio de las Plantas Medicinales (Mexican Institute for the Study of Medicinal Plants). Data contained in this data base have been derived from 41 literature citations primarily concerned with collections of natural history and folkloric claims for Mexican plants. These volumes, which have been computerized, date from 1552 to 1973. We have not been able to document whether current literature is being added to these data. Its primary value is with regard to ethnomedical data

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*See paper by Duke in this volume.

Table 6.—Major Computerized Sources of Scientific and Technical Information on Natural Products

DATA BASE NAME (ACRONYM)	LITERATURE COVERAGE (from)	TYPE DATA RETRIEVABLE	NUMBER OF JOURNAL TITLES REVIEWED	SCOPE OF COVERAGE
AGRICOLA (formerly CAIN)	1970	Literature citations	6,500	Agricultural chemistry and engineering; food and plant science; nutritional data, etc.
BIOSIS Previews	1969	Literature citations	8,000	Life sciences; microbiology; plant and animal sciences; experimental medicine; agriculture; pharmacology; ecology; biochemistry; biophysics.
CAB System	1973	Literature citations + Abstr.	8,000	Agricultural science; plant and animal breeding; plant pathology, nutrition; entomology.
FSTA (Food Sci. & Tech. Abstr.)	1969	Literatue citations + Abstr. summary	1,300	Agricultural chemistry and engineering; food science; economics; patents.
CA SEARCH	1978	Literature citations	14,000	Life sciences; physical sciences
MEDLINE	1974	Literature citations + Abstr. summary	3,000	Life sciences; medical information
IMEPLAM	(a)	Literature citations + Plant use data (b)	41 (c)	Clinical and folklore use; type pharmacological testing; Mexican plants only.
Chinese University of Hong Kong		Literature citations + Abstr. summary		Retrospect and current information on Chinese Traditional medical practices.
NAPRALERT (Natural Products Alert)	1975 (d)	Literature citations + tabular nummerical and textual data from article	8,000	Plant, microbial and animal (primarily marine) chemistry and pharmacology; folklore.

(a). Retrospect information obtained from reference materials and books covering periods from 1552 through 1973.

(b.) Categorical data only no numerical or textual information.

(c.) Fixed bibliography. No indication of current awareness data entry.

(d.) Also includes retrospect data on more than 500 genera of plants extending into the mid-1800's.

systematically presented for a significant number of Mexican plants. Pharmacological testing data in the file are not presented in detail.

Chinese University of Hong Kong. This data base is purported to contain both retrospect and current literature citations as well as brief abstracts of Chinese publications on traditional medical practices. The availability of this data base in the United States has not been established. Nevertheless, the systematic and well organized approach of traditional Chinese medicine makes this data base worth listing as an adjunct to any program for drug development from plants.

Although the literature coverage of these combined databases is quite comprehensive, the inability to compare, correlate, or analyze research data analytically—since they are bibliographic in nature—is a serious drawback of using the data bases in drug or new product development. These data bases provide only lists of citations within the specificity of the search terms—i.e., keyword and/or phrases. If one attempts to be too specific, many citations are overlooked because such specific terms are not used in titles or summary abstracts. On the other hand, broad descriptions within the search terms provide many citations that are not pertinent to new product development research.

Ideally, one would desire a nonbibliographic file that could list and, by computer, compare or correlate real data contained in pertinent citations, then present the data in a digestible tabular form and provide the citation sources. Such nonbibliograhic data files on natural products are not available on-line to the best of our knowledge.

Such a data base does exist off-line. In 1975, NAPRALERT, the acronym for Natural Products Alert, was conceived as a program to overcome the difficulties in using existing files for developing research projects associated with natural products and drug development.

NAPRALERT Content. NAPRALERT, representing a survey of the world literature on natural products, was started in 1975 through a systematic review of each issue of *Chemical Abstracts* and *Biological Abstracts.* Since that time, a large number of retrospect literature searches have been carried out on organisms or subjects of special interest. These retrospect searches cover the literature from the mid 1800's or early 1900's to the present. Approximately one-third of the citations now computerized in NAPRALERT represent these retrospect data. The NAPRALERT database contains information from about 65,000 research reports, books, reviews, patents, and dissertations.

a. **NAPRALERT Data Types.** In addition to bibliographic information, NAPRALERT records the chemical constituents and pharmacological bioassay information from plant, microbial, and animal (primarily marine) extracts. The accepted and synonymous nomenclature of the organism, the parts of the organism used in the study, and the geographic source of the material are also important elements of the data base. In addition to published data, many different indicator codes are used to alert the user that literature is available on the subject or to perform unique sorting capabilities. Another unique, but useful, parameter of the NAPRALERT file, is the recording of ethnomedical, or folkloric, notes as they are encountered in the literature. As a single bit of information, such claims may be of doubtful value, but when correlated with known pharmacologic data or chemical constituents, such data can provide interesting relationships to rationalize the plant's investigation.

b. **NAPRALERT Application.** Two especially important applications of this data base are related to identifying potential sources of useful new products. First, **random** screening of plants can be systematized by an organized computer search and analysis of data to provide a ranked list of the more probable candidates for study prior to any field efforts. Such a methodology was developed using NAPRALERT and was tested for a WHO Task Force assembled to identify indigenous plants potentially useful for human fertility regulation.

In this instance, approximately 4,500 plants were identified as purported to affect fertility, based on folkloric claims or laboratory experiments. To select plants randomly for laboratory investigation from a list this size would not be feasible or cost efficient. Thus it was decided to use the pharmacological data, folklore information, and geographic data contained in the NAPRALERT database as a means of identifying the most promising plants for initial study. After developing appropriate software and subsequently analyzing NAPRALERT-contained data, approximately 300 plants from the list of more than 4,500 were identified as the most promising for study. To date, 50 of these have received preliminary laboratory investigation and eight have confirmed activity using two different laboratory animal assays. Although successful development of a useful clinical drug has not been achieved yet, it seems that such a predictive analysis of appropriate computerized data can be a valuable adjunct to new drug development. In this instance, a list of plants with a predictable area of biological activity was generated by evaluation of the non-bibliographic computerized research data rather than by a costly and time-consuming random field screening process. Certain aspects of the WHO-supported practical application of the NAPRALERT data base have been published (22,54).

A second important application of the information contained in the NAPRALERT file is the ability to present within one computerized report all published folklore information, biological activities—whether assayed in vitro, in animals, or in humans—toxicities, and chemical constituents. In this form, these data can be used effectively to assess potential dangers or suggest safeguards which should be employed when using certain plants. These same data may suggest areas for research on new uses or applications of a specified plant or group of plants. To envision such results only from a stack of publications can be a formidable and frustrating alternative approach.

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THE USDA ECONOMIC BOTANY LABORATORY'S DATA BASE ON MINOR ECONOMIC PLANT SPECIES

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The world is fed mainly by a dozen plant species, and most agricultural countries have specialists for their country's major crops. The world also has thousands of minor economic species, which potentially are as important ecologically and economically as the big dozen, but there are not enough specialists to study them. There is an overwhelming number of climatological, pedological, anthropological, latitudinal, and biological variables associated with these minor species. The Economic Botany Laboratory (EBL) of the U.S. Department of Agriculture (USDA) is trying to gather data on these potentially economically useful species.

In 1971, USDA asked me to develop an information system on potential alternative crops for narcotics. With no computers available, I set up a manual information retrieval system of transparencies for screening 1,000 economic plants as potential substitutes. In 1972, I was encouraged to abandon the transparencies for computers. Now, 10 years later, there are many data in the computer. However, the computer bill for 1981 was over $50,000, and with the loss of our support from the National Cancer Institute, we can no longer afford to keep the data bases online.

Data Base Files and Subsets

Some of our files and their subsets are listed below, subjectively ranked in decreasing order of importance to USDA's Beltsville Agricultural Research Center.

1. ECOSYSTEMATICS
    - Germ Plasm Donor Subset (mailing list)
    - Monthly Temperature
    - Monthly Precipitation
    - Soil pH
    - Soil Type (limited)
    - Salinity (more limited)
    - Tolerances (not computerized)
2. YIELD
    - Phytomass Subset
    - Cultural Subsets
3. CLIMATE
    - Wernstedt
    - Questionnaires
    - Publishing Experiment Stations
4. NUTRITION
    - Food Composition Tables
    - Watt and Merrill
    - Wealth of India
    - Miller (1958)
    - Gohl (1981)
    - ZERO-MOISTURE SUBSET
5. AGROFORESTRY
    - Ecology Subset
    - Germination Subset
    - Cultural Subset
    - Nutrition Subset
    - Utilization Subset
    - Yield Subset
    - Wood Characterization Subset
    - Pest Subset
    - INTERCROPPING
6. PEST (fungi and insects only)
7. ETHNOMED
    - Colloquial Name Subset
    - Pesticide Subset
    - Pharmacologically Proven Subset
    - Cancer Subset
    - Malaria Subset
    - Geography Subset
    - Ailment Subset
    - Source

Methods and Results

Ecosystematic File

One of our most productive activities was mailing over 1,000 questionnaires worldwide to scientists and extension people, intentionally emphasizing developing countries. Within 2 years, over 500 people had responded, sending published and unpublished ecosystematic data (annual rainfall, annual temperature, soil type, soil pH, elevation, etc.) on economic plants and some weeds and nitrogen-fixing species. These data, related to about 1,000 species, now are incorporated in the Ecosystematic File (fig. 1) and are tabulated in *The Quest for Tolerant Germplasm* (4).

A success story addressing the multimillion-dollar problem of iron-efficient sorghum germ plasm illustrates the potential value of the ecosystematic file in seeking germ plasm for extreme environments (6). Scientists from the Plant Stress Laboratory were incredulous at the high soil pH reported for *Sorghum bicolor* in the file. Most sorghums are chlorotic and nonproductive on alkaline soils. The scientists asked for more information on the high pH sorghum. Since each species in the file is recorded with the name and address of the reporting scientist(s), the computer was able to provide a mailing list of 14 correspondents who reported sorghum at pH 7.5 or higher. Letters were sent to 10 of the correspondents. Four responded with seed, two lots of which were iron-efficient sorghum which grows and produces without chlorosis on alkaline soils in the Western United States. Now we are cooperating with the USDA Plant Physiology Institute in a search for soybeans tolerant to aluminum toxicity.

Figure 1.—Sample Page From "The Quest For Tolerant Germplasm"

Sesamum radiatum	Wild sesame		Tm	P,H	4.3-5.0	25-40	25-27	AF	64
Sesbania bispinosa	Canicha	Wm	Tvm	A,S	4.3-7.5	6-33	16-29	HI	12,24
Sesbania exaltata	Hemp sesbania	Wm	Tdm	P,A,H	4.5-7.3	7-25	13-27	NA	12
Setaria italica	Italian millet	Cmw	Tvw	A,G	5.0-8.3	3-42	6-27	CJ	18
Setaria sphacelata	Golden timothy	Cdm	Tvm	P,G	4.3-7.1	7-33	11-27	AF	18,36,54
Sicana odorifera	Casabanana	Sdm	Tvm	P,V	5.0-8.0	7-28	21-25	SA	
Simarouba glauca	Aceituna	Sm	Tdm	P,S,T	5.3-8.0	11-25	21-27	MA	
Simmondsia chinensis	Jojoba	Wxt	Td	P,S,T	7.3-8.2	2-11	16-26	MA	56,±100
Sinapis alba	White mustard	Bmw	Td	A,H	4.5-8.0	4-18	5-24	ME	24
Smilax aristolochiifolia	Sarsaparilla	Wm	Sm	P,S,L		17	18-23	MA	
Solanum aethiopicum	Mock tomato	Cm	Tm	P,S	6.2-6.2	9-40	9-25	AF	24
Solanum aviculare	Australian nightshade	Cmw	Wdm	P,S,T	5.5-8.2	7-13	12-17	AU	46,48,92
Solanum ferox	Ram-begun	Cm	Tw	P,H	4.5-5.0	7-42	83-27	HI,II	24
Solanum gilo	Gilo		Tm	P,S	4.3-4.8	27-33	26-27	AF	24
Solanum hyporhodium	Cocona		Sdw	P,S	6.5-7.3	7-31	21-23	SA	
Solanum incanum	Sodom apple		Sdm		5.5-7.8	8-17	19-23	AF,HI	24
Solanum indicum	Indian nightshade	Sdm	Txw		4.3-7.8	2-42	19-27	HI,II	24
Solanum khasianum	Solanum khasianum	Cw	Wm	H	5.0-6.0	9-13	13-15	HI	24
Solanum laciniatum	Kangaroo apple	Cmw	Wd	P/A,S,T	5.6-8.2	7-11	12-15	AU	48,92
Solanum macrocarpon	Native eggplant	Ww	Tdm	H,S	4.3-5.2	13-37	18-27	AF	36
Solanum melongena	Eggplant	Csw	Txw	P/A,H	4.3-8.7	2-42	7-28	CJ,HI	24,36,48
Solanum muricatum	Melon-pear	Sdm	Td	P,S	5.7-7.3	7-15	18-25	SA	24
Solanum nigrum	Black nightshade	Bw	Txw	A,H	4.3-8.4	2-42	5-27	AF,ES	24,36,48
Solanum quitoense	Lulo	Cmw	Td	P,H,S	5.8-8.0	7-31	11-25	SA	24
Solanum torvum	Terongan	Cm	Tvw		4.3-8.7	7-42	9-29	MA,HI	24
Solanum tuberosum	Potato	Bmw	Tvw	A,H	4.2-8.3	3-46	4-27	SA,MA,ES	24,36,48
Solenostemon rotundifolius	Hausa potato	Sm	Td	P,H	5.0-5.0	13-17	23-26	AF	±84
Sorghastrum avenaceum	Indiangrass	Wm	Td	P,G	5.6-7.1	11-17	12-26	NA	
Sorghum X almum	Almum sorghum	Csw	Tvd	P,G	5.0-8.3	3-25	9-26	SA	40
Sorghum bicolor	Sorghum	Csw	Ttw	A,G	4.3-8.7	4-41	8-27	CJ,HI,ME	20

† For authorities on most of these species, see Duke and Terrell (1974).

‡ Following Holdridge (1947); T-Tropical, S-Subtropical, W-Warm Temperate, C-Cool Temperate, B-Boreal; x-Desert, t-Thorn, s-Steppe, v-Very Dry, d-Dry, m-Moist, w-Wet, and r-Rain.

§ A-Annual, B-Biennial, P-Perennial, P/A-Perennial treated as an annual, H-Herb, G-Grass, L-Liana (woody vine), S-Shrub, T-Tree, V-Herbaceous vine.

¶ Average of monthly means with values below 0°C treated as 0.

Center of diversity, based largely on Zeven and Zhukovsky (1975) and Plant Taxonomy files. The first symbol cited is possibly a center of origin. CJ-China-Japan, II-Indochina-Indonesia, AU-Australia, HI-Hindustani, CE-Central Asia, NE-Near East, ME-Mediterranean, AF-Africa, ES-Eurosiberian, SA-South America, MA-Middle America, NA-North America. For space conservation, no more than three centers are listed.

†† Diploid chromosome numbers based largely on Fedorov (1969), Zeven and Zhukovsky (1975), and unpublished compilation by MacHenry Stiff. Only three counts are listed here, but many more may have been reported.

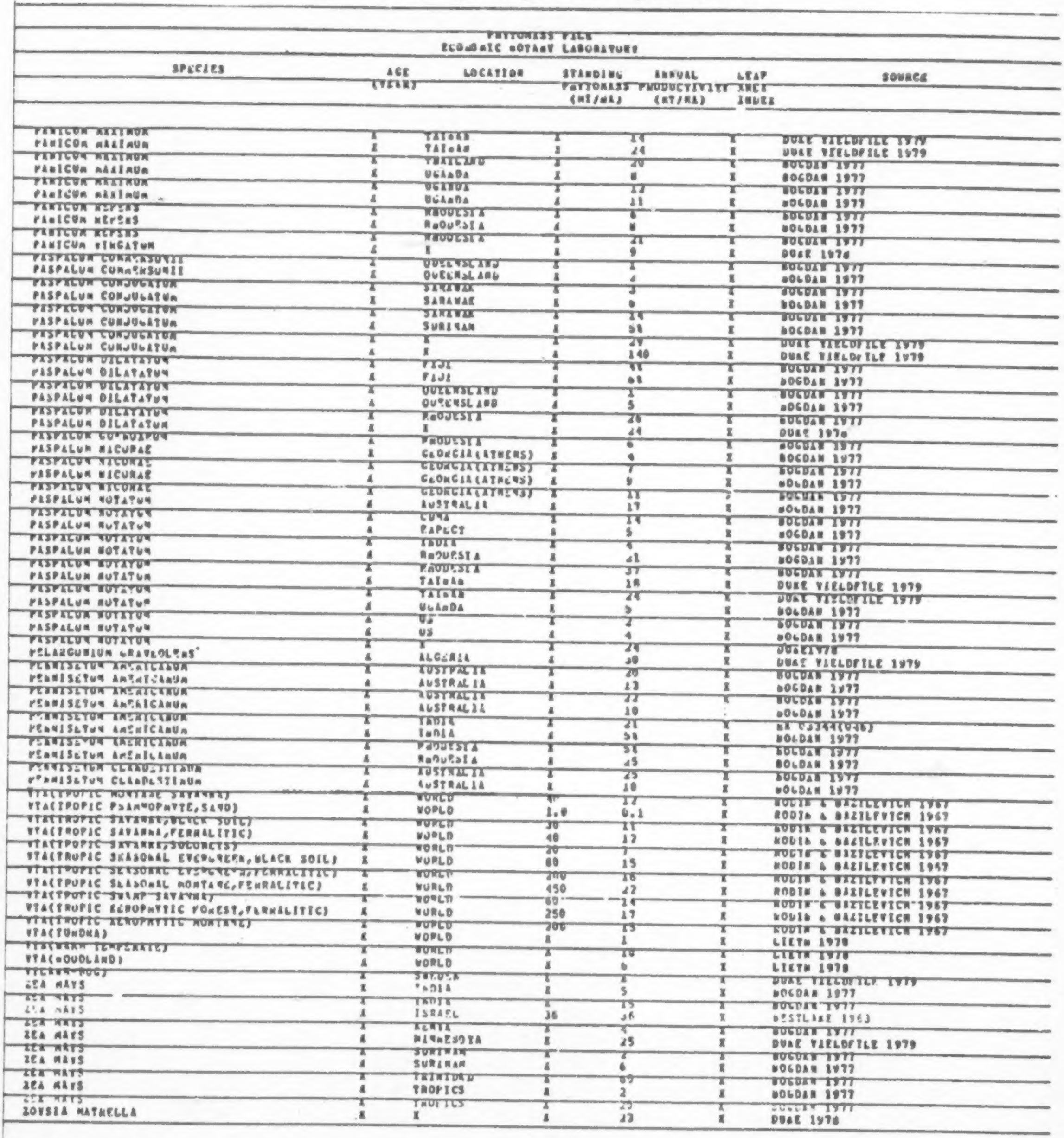
SOURCE: Duke, J. A., "The Quest For Tolerant Germplasm," ch. 1, pp. 1-61, *ASA Special Symposium 32* "Crop Tolerance to Suboptimal Land Conditions" (Madison, Wis.: American Society of Agronomy, 1978).

Yield File

In addition to data from the questionnaires, data from publications of experiment stations have been entered into the Yield File. We regret that we cannot keep up with this literature; the entries probably account for less than 1 percent of the yield data published annually by experiment stations. By increasing the data included in this file, which is impossible at our current level of funding, people could be told the yield of exotic crops (with various cultural inputs) grown in areas ecologically similar to theirs. The Yield File is clean and useful now, though off-line. With major backing, it could help strategists predict yields of new crops in particular areas.

For a brief period, funding was available to promote one subset of the file, the Phytomass File (fig. 2). (Phytomass is defined as aboveground dry-matter yields of plants.) Department of Energy (DOE) support for that file has been discontinued, but some institutions such as DOE or Oak Ridge may have similar files. Data from the Phytomass File support our early contention that C_4 grasses are roughly twice as productive as C_3 grasses, which are in turn roughly twice as productive as legumes. Availability of this kind of information could save

Figure 2.—Sample Page From Phytomass File



PHYTOMASS FILE
ECONOMIC BOTANY LABORATORY

SPECIES	AGE (YEAR)	LOCATION	STANDING PHYTOMASS (MT/HA)	ANNUAL PRODUCTIVITY (MT/HA)	LEAF AREA INDEX	SOURCE
PANICUM MAXIMUM	X	TAIWAN	X	14	X	DUKE YIELDFILE 1979
PANICUM MAXIMUM	X	TAIWAN	X	24	X	DUKE YIELDFILE 1979
PANICUM MAXIMUM	X	THAILAND	X	20	X	BOGDAN 1977
PANICUM MAXIMUM	X	UGANDA	X	8	X	BOGDAN 1977
PANICUM MAXIMUM	X	UGANDA	X	12	X	BOGDAN 1977
PANICUM MAXIMUM	X	UGANDA	X	11	X	BOGDAN 1977
PANICUM REPENS	X	RHODESIA	X	6	X	BOGDAN 1977
PANICUM REPENS	X	RHODESIA	X	8	X	BOGDAN 1977
PANICUM REPENS	X	RHODESIA	X	21	X	BOGDAN 1977
PANICUM VIRGATUM	X	X	X	9	X	DUKE 1978
PASPALUM COMMERSONII	X	QUEENSLAND	X	1	X	BOGDAN 1977
PASPALUM COMMERSONII	X	QUEENSLAND	X	4	X	BOGDAN 1977
PASPALUM CONJUGATUM	X	SARAWAK	X	3	X	BOGDAN 1977
PASPALUM CONJUGATUM	X	SARAWAK	X	8	X	BOGDAN 1977
PASPALUM CONJUGATUM	X	SARAWAK	X	14	X	BOGDAN 1977
PASPALUM CONJUGATUM	X	SURINAM	X	58	X	BOGDAN 1977
PASPALUM CONJUGATUM	X	X	X	29	X	DUKE YIELDFILE 1979
PASPALUM CONJUGATUM	X	X	X	140	X	DUKE YIELDFILE 1979
PASPALUM DILATATUM	X	FIJI	X	44	X	BOGDAN 1977
PASPALUM DILATATUM	X	FIJI	X	68	X	BOGDAN 1977
PASPALUM DILATATUM	X	QUEENSLAND	X	1	X	BOGDAN 1977
PASPALUM DILATATUM	X	QUEENSLAND	X	5	X	BOGDAN 1977
PASPALUM DILATATUM	X	RHODESIA	X	26	X	BOGDAN 1977
PASPALUM DILATATUM	X	X	X	24	X	DUKE 1978
PASPALUM [illegible]	X	RHODESIA	X	6	X	BOGDAN 1977
PASPALUM NICURAE	X	GEORGIA(ATHENS)	X	4	X	BOGDAN 1977
PASPALUM NICURAE	X	GEORGIA(ATHENS)	X	7	X	BOGDAN 1977
PASPALUM NICURAE	X	GEORGIA(ATHENS)	X	9	X	BOGDAN 1977
PASPALUM NICURAE	X	GEORGIA(ATHENS)	X	11	X	BOGDAN 1977
PASPALUM NOTATUM	X	AUSTRALIA	X	17	X	BOGDAN 1977
PASPALUM NOTATUM	X	CUBA	X	14	X	BOGDAN 1977
PASPALUM NOTATUM	X	EGYPT	X	5	X	BOGDAN 1977
PASPALUM NOTATUM	X	INDIA	X	4	X	BOGDAN 1977
PASPALUM NOTATUM	X	RHODESIA	X	41	X	BOGDAN 1977
PASPALUM NOTATUM	X	RHODESIA	X	37	X	BOGDAN 1977
PASPALUM NOTATUM	X	TAIWAN	X	18	X	DUKE YIELDFILE 1979
PASPALUM NOTATUM	X	TAIWAN	X	24	X	DUKE YIELDFILE 1979
PASPALUM NOTATUM	X	UGANDA	X	5	X	BOGDAN 1977
PASPALUM NOTATUM	X	US	X	2	X	BOGDAN 1977
PASPALUM NOTATUM	X	US	X	4	X	BOGDAN 1977
PASPALUM NOTATUM	X	X	X	24	X	DUKE1978
PELARGONIUM GRAVEOLENS	X	ALGERIA	X	30	X	DUKE YIELDFILE 1979
PENNISETUM AMERICANUM	X	AUSTRALIA	X	20	X	BOGDAN 1977
PENNISETUM AMERICANUM	X	AUSTRALIA	X	13	X	BOGDAN 1977
PENNISETUM AMERICANUM	X	AUSTRALIA	X	22	X	BOGDAN 1977
PENNISETUM AMERICANUM	X	AUSTRALIA	X	10	[illegible]	BOGDAN 1977
PENNISETUM AMERICANUM	X	INDIA	X	21	X	HA C3344(036)
PENNISETUM AMERICANUM	X	INDIA	X	58	X	BOGDAN 1977
PENNISETUM AMERICANUM	X	RHODESIA	X	51	X	BOGDAN 1977
PENNISETUM AMERICANUM	X	RHODESIA	X	45	X	BOGDAN 1977
PENNISETUM CLANDESTINUM	X	AUSTRALIA	X	25	X	BOGDAN 1977
PENNISETUM CLANDESTINUM	X	AUSTRALIA	X	10	X	BOGDAN 1977
VTA(TROPIC MONTANE SAVANNA)	X	WORLD	40	12	X	RODIN & BAZILEVICH 1967
VTA(TROPIC PSAMMOPHYTE,SAND)	X	WORLD	1.8	0.1	X	RODIN & BAZILEVICH 1967
VTA(TROPIC SAVANNA,BLACK SOIL)	X	WORLD	30	11	X	RODIN & BAZILEVICH 1967
VTA(TROPIC SAVANNA,FERRALITIC)	X	WORLD	40	12	X	RODIN & BAZILEVICH 1967
VTA(TROPIC SAVANNA,SOLONETS)	X	WORLD	20	7	X	RODIN & BAZILEVICH 1967
VTA(TROPIC SEASONAL EVERGREEN,BLACK SOIL)	X	WORLD	80	15	X	RODIN & BAZILEVICH 1967
VTA(TROPIC SEASONAL EVERGREEN,FERRALITIC)	X	WORLD	200	16	X	RODIN & BAZILEVICH 1967
VTA(TROPIC SEASONAL MONTANE,FERRALITIC)	X	WORLD	450	22	X	RODIN & BAZILEVICH 1967
VTA(TROPIC SWAMP SAVANNA)	X	WORLD	60	14	X	RODIN & BAZILEVICH 1967
VTA(TROPIC XEROPHYTIC FOREST,FERRALITIC)	X	WORLD	250	17	X	RODIN & BAZILEVICH 1967
VTA(TROPIC XEROPHYTIC MONTANE)	X	WORLD	200	15	X	RODIN & BAZILEVICH 1967
VTA(TUNDRA)	X	WORLD	X	1	X	LIETH 1978
VTA(WARM TEMPERATE)	X	WORLD	X	10	X	LIETH 1978
VTA(WOODLAND)	X	WORLD	X	6	X	LIETH 1978
[illegible]	X	[illegible]	X	[illegible]	X	DUKE YIELDFILE 1979
ZEA MAYS	X	INDIA	X	5	X	BOGDAN 1977
ZEA MAYS	X	INDIA	X	15	X	BOGDAN 1977
ZEA MAYS	X	ISRAEL	36	36	X	WESTLAKE 1963
ZEA MAYS	X	KENYA	X	5	X	BOGDAN 1977
ZEA MAYS	X	MINNESOTA	X	25	X	DUKE YIELDFILE 1979
ZEA MAYS	X	SURINAM	X	2	X	BOGDAN 1977
ZEA MAYS	X	SURINAM	X	6	X	BOGDAN 1977
ZEA MAYS	X	TRINIDAD	X	69	X	BOGDAN 1977
ZEA MAYS	X	TROPICS	X	2	X	BOGDAN 1977
ZEA MAYS	X	TROPICS	X	25	X	BOGDAN 1977
ZOYSIA MATRELLA	X	X	X	23	X	DUKE 1978

VT = Vegetation Type, VTA = Vegetation Type Average

X = Assumes Dry Matter

(DM) = 10% Wet Weight. All data reported as DM

X = No data available

Under Source, HA = Herbage Abstract

SOURCE: Duke, J. A., "The Gene Revolution," paper No. 1, pp. 89-150, Office of Technology Assessment, Background papers for *Innovative Biological Technologies For Lesser Developed Countries* (Washington, D.C.: U.S. Government Printing Office, 1981).

countless hours and dollars in screening projects where maximum biomass production is a priority.

Climate File

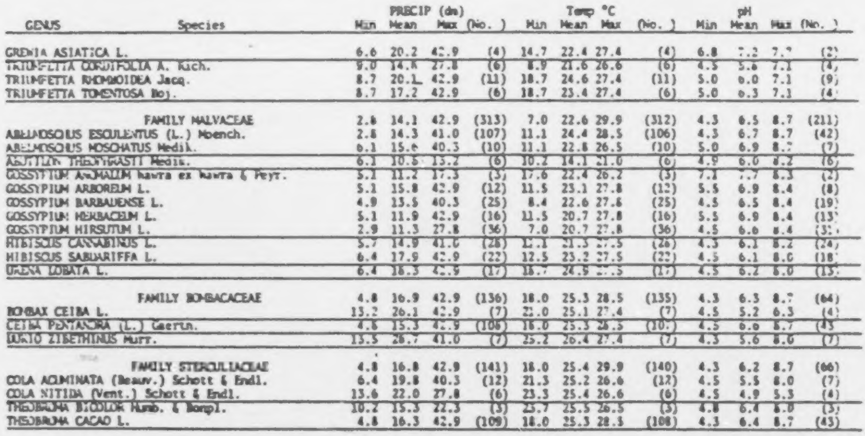
The easiest file acquired was the Climate File. It is the computer tape to Wernstedt's *World Climatic Data* (1972) and was purchased for less than $200. USDA colleagues have converted the temperature data from fahrenheit to centigrade, and the rainfall and elevation to metric units. The monthly means for these 18,000 stations now are compatible with hundreds of climatic figures gathered through questionnaires and publications. Monthly precipitation and temperature data for about 20,000 stations now are integrated into the Climate File. A species' ecological amplitude can be determined by using this file in conjunction with ecological data for geographical areas from which the species is reported. For example, if one wanted to know the ecological amplitudes of a species that is not in the Ecosystematic File, one could consult herbaria and publications for locales where the plant grows, choose those that occur in the Climatic File and, using the computer, obtain climatic highs, lows, and means of these areas. Further, one could pick potential germ plasm sources that are most similar ecologically to the germ plasm recipient. This important germ plasm matching capability applies not only to minor, underused economic plants but to cultivars and varieties of the big dozen. A sample page from an early version of an economic amplitude paper appears in figure 3. This file has been used in the USDA Plant Physiology Institute at Beltsville by colleagues who are interested in the tropicality of members of the Malvaceae. They are studying the distribution of malvalic acid, an acid possibly involved in responses to temperature stress in cold- and heat-tolerant mallows.

In a seminar at Beltsville on March 17, 1982, Dr. G. L. Stebbins introduced a list of cold-tolerant to heat-tolerant legumes, speculating that the greater the DNA volume, the greater the cold tolerance. Without consulting the *Handbook of Legumes of World Economic Importance* (5), wherein the ecosystematic amplitudes of species are published, I predicted that the legumes' mean annual temperatures would line up inversely with Stebbins' DNA prediction. The lineup was almost perfect, as depicted:

	DNA volume (from Stebbins seminar)	*Mean temperature ° C (from Handbook of Legumes)*
Vicia faba	26.7	12.1
Pisum sativum	9.8	12.9
Phaseolus vulgaris	3.7	19.3
Glycine max	2.2	18.2
Lablab purpureus	0.7	21.9

The Climatic File can be used to address problems in the global carbon cycle. Tropical forests play an important role in the global carbon cycle because they store 46 percent of the world's terrestrial carbon pool (1). Brown and Lugo presented data for each of several Holdridge Life Zones, projecting total forest biomass, soil carbon content, net carbon content, net primary production, wood production, and leaf litter production. The EBL has formulae for converting its 20,000 climatic data sites into Holdridge Life Zones and, using a computer,

Figure 3.—Sample Page Showing Ecosystematic Data For Malvaceae



GENUS Species	PRECIP (dm) Min	Mean	Max	(No.)	Temp °C Min	Mean	Max	(No.)	pH Min	Mean	Max	(No.)
GREWIA ASIATICA L.	6.6	20.2	42.9	(4)	14.7	22.4	27.4	(4)	6.8	7.2	7.7	(2)
TRIUMFETTA CORDIFOLIA A. Rich.	9.0	14.8	27.8	(6)	8.9	21.6	26.6	(6)	4.5	5.6	7.1	(4)
TRIUMFETTA RHOMBOIDEA Jacq.	8.7	20.1	42.9	(11)	18.7	24.6	27.4	(11)	5.0	6.0	7.1	(9)
TRIUMFETTA TOMENTOSA Boj.	8.7	17.2	42.9	(6)	18.7	23.4	27.4	(6)	5.0	6.3	7.1	(4)
FAMILY MALVACEAE	2.6	14.1	42.9	(313)	7.0	22.6	29.9	(312)	4.3	6.5	8.7	(211)
ABELMOSCHUS ESCULENTUS (L.) Moench.	2.8	14.3	41.0	(107)	11.1	24.4	28.5	(106)	4.3	6.7	8.7	(42)
ABELMOSCHUS MOSCHATUS Medik.	6.1	15.6	40.3	(10)	11.1	22.8	26.5	(10)	5.0	6.9	8.7	(7)
ABUTILON THEOPHRASTI Medik.	6.1	10.5	13.2	(6)	10.2	14.1	21.0	(6)	4.9	6.0	8.2	(6)
GOSSYPIUM ANOMALUM Wawra ex Wawra & Peyr.	5.1	11.2	17.3	(3)	17.6	22.4	26.2	(3)	7.1	7.7	8.3	(2)
GOSSYPIUM ARBOREUM L.	5.1	15.8	42.9	(12)	11.5	23.1	27.8	(12)	5.5	6.9	8.4	(8)
GOSSYPIUM BARBADENSE L.	4.9	13.5	40.3	(25)	8.4	22.6	27.6	(25)	4.5	6.5	8.4	(19)
GOSSYPIUM HERBACEUM L.	5.1	11.9	42.9	(16)	11.5	20.7	27.8	(16)	5.5	6.9	8.4	(13)
GOSSYPIUM HIRSUTUM L.	2.9	11.3	27.8	(36)	7.0	20.7	27.8	(36)	4.5	6.6	8.4	[illegible]
HIBISCUS CANNABINUS L.	5.7	14.9	41.0	(26)	12.1	21.3	27.5	(26)	4.3	6.1	8.2	(24)
HIBISCUS SABDARIFFA L.	6.4	17.9	42.9	(22)	12.5	23.2	27.5	(22)	4.5	6.1	8.0	(18)
URENA LOBATA L.	6.4	16.3	42.9	(17)	16.7	24.5	27.5	(17)	4.5	6.2	8.0	(15)
FAMILY BOMBACACEAE	4.8	16.9	42.9	(136)	18.0	25.3	28.5	(135)	4.3	6.3	8.7	(64)
BOMBAX CEIBA L.	13.2	26.1	42.9	(7)	22.0	25.1	27.4	(7)	4.5	5.2	6.3	(4)
CEIBA PENTANDRA (L.) Gaertn.	4.8	15.3	42.9	(106)	18.0	25.3	28.5	(105)	4.5	6.6	8.7	(43)
DURIO ZIBETHINUS Murr.	13.5	26.7	41.0	(7)	25.2	26.4	27.4	(7)	4.3	5.6	8.0	(7)
FAMILY STERCULIACEAE	4.8	16.8	42.9	(141)	18.0	25.4	29.9	(140)	4.3	6.2	8.7	(66)
COLA ACUMINATA (Beauv.) Schott & Endl.	6.4	19.8	40.3	(12)	21.3	25.2	26.6	(12)	4.5	5.5	8.0	(7)
COLA NITIDA (Vent.) Schott & Endl.	13.6	22.0	27.8	(6)	23.3	25.4	26.6	(6)	4.5	4.9	5.3	(4)
THEOBROMA BICOLOR Humb. & Bonpl.	10.2	15.3	22.3	(3)	23.7	25.5	26.5	(3)	4.8	6.4	8.0	(3)
THEOBROMA CACAO L.	4.8	16.3	42.9	(109)	18.0	25.3	28.5	(108)	4.3	6.4	8.7	(43)

SOURCE: Duke, J. A., "Ecosystematic Data on Economic Plants," *Quart. J. Crude Res.* 17, No. 3-4, 1979, pp. 91-110.

can generate Holdridge Life Zone maps for countries not now mapped in the Holdridge system. We then could project standing biomass, total carbon, and annual productivity of the zonal forests, based on Brown and Lugo's numbers or refinements thereof, and give real or projected yield figures for high-biomass grasses, energy-tree plantations, or conventional crops for these Holdridge Life Zones. This could provide some guidelines for choosing the best crop-agroforestry combinations for agricultural development in Third World countries.

We believe that the climate of some remote area can be deduced by checking the ecological amplitudes of dozens of perennials growing there better than by measuring the rainfall and temperature for 1 year. The fig, scuppernong, and pecan at my Howard County farm are near their northern productive limits; the ginseng, rhubarb, and sugar maple near their southern productive limits. Based on these species, the mean temperature at my farm can be predicted to be between 11° and 13° C.

Dr. Peter Raven, director of the Missouri Botanical Gardens, asked us at what locations in the world the climate was most similar to that of the Missouri Botanical Garden. If asked simply for annual temperature and annual precipitation, the computer would indicate many places that do not have the temperature extremes of St. Louis' continental climate. Introductions from maritime climates with identical mean temperatures might be killed by the summer heat and/or winter cold of St. Louis. A continentality variable, which will differentiate among climates with similar mean annual temperatures but different vegetational potential, has been added to the Climate File.

In October 1982, EBL was asked to name locales in Latin American where date palm would grow. As a test case, Dr. Atchley at USDA and I each devoted no more than 4 hours to this query (app. I and II). The difference in conclusions reached is due to Dr. Atchley's assuming rainfed conditions and basing his projection on actual reports for date palm, and my assuming an irrigated situation because artifical or subsurface irrigation is implicit in most of the good date-growing areas I cite. The computer provided lists of possible sites for date palm under both irrigated and rainfed conditions, and eliminated hours of searching through 20,000 climatic data points.

The narcotic-replacement program led us to the *coqueros*, the cocaine-leaf chewers of the Andes. The coca leaves chewed by these Andean Indians are high in calcium and iron, more so than any plant food in the Food Composition Table for Latin America (fig. 4a). Calcium and iron, as well as certain vitamins and proteins, often are deficient in diets of the farmers we were trying to divert from cultivating the coca ("cocaine") bush. The problem, therefore, was one of both nutrition and crop substitution. What commercial food crops could the farmer grow as substitutes for coca? To answer this, we needed to know their climate. However, they might be 100 miles and 10 mountain ranges away from the nearest climatic recording station (that ceased recording 10 years ago). This quandary spawned our Ecological Amplitudes of Weeds program. We added weeds to our questionnaires to help predict climate in remote areas (fig. 5). Another use of the Ecological Amplitudes of Weeds program is in mapping the potential for an alien weed to spread in the United States. Determining ecological amplitudes of a weed by consulting its distribution and extracting climatic data from the Climate File, we can determine where in the U.S. the climate is most closely and least closely matched.

Nutrition File

For the Nutrition File, we used at least one credible entry for each plant species in Food Composition Tables for East Asia, Africa, and Latin America, from Watt and Merrill's *Composition of Foods* (Agriculture Handbook No. 8) and from *The Wealth of India* (C.S.I.R., 1948-76), computerizing the proximate analyses of hundreds of botanicals. I scored the plants' nutritive contents (elements, vitamins, calorie and fiber content) as extremely low (E), low (L), high (H), or very high (V), relative to USDA's recommended dietary allowance (RDA) (fig. 4b). Unfortunately, I had overlooked Miller's *Composition of Cereal Grains and Forages* (1958), which consolidated thousands of forage plant analyses. No sooner had I finished adding this information than another massive compilation with numerous new data on forage analyses was published (7). My colleagues at USDA and I are entering these data into the computer file which we hope will be tabulated and published by CRC next year.

We devised a computer program to convert our as-purchased proximate analysis file to a zero-moisture basis (fig. 6). To ensure that only complete proximate analyses are used, the computer uses only those columns for which the sum of water, protein, carbohydrates, fibers, and ash is 100 percent (±1). The computer then multiplies all columns except water by 100 ÷ (100=x), where x

Figure 4A.—Nutritional Composition of Coca

Nutritional Comparison per 100 g of Coca Leaves with other Latin American Plant Foods.

FOOD ITEM	# in sample	Cal	H_2O g	Prot. g	Fat g	Carb. g	Fiber g	Ash g	Ca mg	P mg	Fe mg	Vit A[1] IU	Thia mg	Rib mg	Nia mg	Vit C mg
San Francisco coca	(1)	305	6.5	18.9	5.0	46.2	14.4	9.0	1540	911	45.8	11,000	0.35	1.91	1.29	1.4
Bolivia coca	(3)	—[2]	8.8	—	1.6	42.4	8.0	5.3	—	—	—	—	—	—	—	—
Peru coca	(3)	—	10.3	18.7	—	—	17.5	4.6	2038	363	7.9	9,000	0.81	1.55	6.17	—
COCA AVERAGE	(7)	—	8.5	18.8	3.3	44.3	13.3	6.3	1789	637	26.8	10,000	0.58	1.73	3.7	1.4
PLANT FOOD AVERAGE	(50)	279	40.0	11.4	9.9	37.1	3.2	2.0	99	270	3.6	135	0.38	0.18	2.2	13.0
Nuts & Seeds	(10)	521	9.9	16.8	36.0	28.2	3.6	3.1	273	522	4.3	17	0.78	0.28	5.2	2.1
Pulses	(10)	354	11.3	25.4	5.0	55.1	5.5	3.3	102	398	7.1	20	0.58	0.24	2.25	1.9
Cereals	(10)	352	11.5	11.7	3.7	71.0	4.0	2.1	74	346	4.8	13	0.41	0.25	2.7	0.8
Vegetables	(10)	74	87.3	1.8	0.4	16.9	1.5	0.9	26	52	1.2	595	0.09	0.05	1.0	31.0
Fruits	(10)	93	79.6	1.2	4.5	14.1	1.4	0.7	20	33	0.8	35	0.05	0.06	0.08	29.0

SOURCE: Duke, J. A., Aulik, D., and Plowman, T. "Nutritional Value of Coca," Botanical Museum Leaflets, vol. 24, No. 6, (Boston, Mass.: Harvard University, 1975), pp. 113-119.

equals water percentage. The completely new and unique table has hundreds of species compared on a zero-moisture basis. The Nutrition File (as purchased or zero-moisture) can be linked through a species' scientific name to the Yield File to convert yields to protein per hectare instead of grain per hectare, and to the Ecosystematic File to show which will yield the most leaf protein per hectare under any specified combination of annual temperature, annual precipitation, soil pH, etc.

Before the National Cancer Institute discontinued its support for the EBL data base, we started a file on biologically active compounds to parallel the Nutrition File. It indicated the toxic compounds and their LD50's for plant genera (fig. 7). We regret that other quantitative data were omitted. Dr. Farnsworth's comprehensive NAPRALERT program dwarfs our attempt at computerizing biologically active compounds in plants. Since he also uses plants' scientific names, his pharmacological data could be sorted against any one or all of our data files, using the scientific names to link the two data bases.

Ethnomed File

It is ironic that the Ethnomed File (fig. 8), with which I worked most closely for nearly 5 years, is now the lowest priority file. The file was built to encourage Third World countries to supply medicinal and poisonous plants for a collaborative screening program with the U.S. National Cancer Institute. With 88,000 entries, the Ethnomed File is probably the largest extant computerized data base for folk cancer remedies and is quite good for general folk remedies. Pesticidal activities, of greater current interest to USDA, also are included (see fig. 9 for insecticide subset sample). This file can interact with any other file through the same scientific name.

Ethnomed is not dead; it lives on as a much consulted printout. For example, we have been asked to help an NIH contractor prepare a prioritized list of Nigerian species for antimalarial screening (fig. 8). The malaria entries marked with an asterisk contain compounds with proven antimalarial activity. The species marked with a double asterisk correct or alleviate malaria. Unfortunately, the common name file is incomplete. It would be useful to many agencies, since many plants are recorded by common rather than scientific name. Interlocking scientific names with the name of a country from the Ecosystematic File should show not only which antimalarial species occur in that country but should give the names and addresses of the people who reported them. Using the ecosystematic amplitudes of the target species, the computer could indicate the country's climatic stations within the ecological ranges of the target species. For example, the computer could name many antimalarial species occurring in Nigeria and list villages suitable as staging areas to search for the species.

Figure 4B.—Sample Page From Vegetarian Vitachart

Common Name and plant part[1]	Scientific Name[2]	Calcium	Calories	Fiber	Iron	Magnesium	Niacin	Phosphorus	Potassium	Protein	Riboflavin	Sodium	Thiamin	Vitamin A	Vitamin C
wild grape (f)	Vitis tiliifolia	L	L	H	H		L	L		L	L		L	E	H
wild lettuce (1)	Lactuca taraxacifolia	H	L	H				L		L					
wild mango (f)	Irvingia gabonensis	L	L	L	H			L		L					V
wild plum (f)	Bequaertiodendron magalismontanum	L	L	H	L		L	L		L	L		L		H
wild rice	Zizania aquatica	L	H	H	H	H	H	H	L	H	H	E	H	E	E
willowleaf Lucuma	Lucuma salicifolia	L	L	H	L		H	L		L	E		H	L	H
wine palm	Mauritia vinifera	H	L	V	H		L	L		L	H		L	V	H
winged yam	Dioscorea alata	L	L	L	L		L	L	H	L	L	E	L	E	H
winged yam	Dioscorea alata	L	L	H	L		L	L		L	L		L	E	H
wintersquash (f)	Cucurbita maxima	L	L	L	L		L	L	H	L	L	E	L	H	H
wintersquash (1)	Cucurbita maxima	H	L	H	L		L	H	H	L	H	E	L	H	H
wintersquash (fl)	Cucurbita maxima	H	E	L	H		L	L	L	L	L	E	L	L	H
wolfberry (d, f)	Lycium chinensis	L	H	V	V		H	H	H	H	V	L	H	V	V
wolfberry (1)	Lycium chinensis	H	L	H	H		L	L	H	L	H	L	L	V	H
wood oil nut	Ricinodendron heudelotii	H	H	H	L		E	V		H	E		E	E	E
wooly manzanita	Arctostaphylos tomentosa		L	H			L	L		L	E		L	H	V
wormseed (1)	Chenopodium ambrosioides	H	L	H	H		L	L		L	H		L	H	H
yam	Dioscorea sp.	L	L	L	L		L	L	H	L	L		L	E	H
yambean (r)	Pachyrrhizus angulatus	E	L	H	L		L	L		L	L		L	E	H
yambean (tuber)	Sphenostylis stenocarpa	L	L	L				H		L					
yambean (r)	Pachyrrhizus sp.	L	L	L	L		L	L		L	L		L	E	H
yardlong pea (pod)	Vigna unguiculata	L	L	H	L		L	L	L	L	L	E	L	L	H
yardlong pea (1)	Vigna unguiculata	H	L	H	H		L	H	H	L	H	E	H	H	H
yautia (1)	Xanthosoma sp.	H	L	H	H			H		L				V	H
yautia (r)	Xanthosoma sp.	L	L	H	L			L		L					H
yebbnut (s)	Cordeauxia edulis	L	H	H	H			H		H					
yellow hogplum (f)	Spondias mombin	E	L	L	E		L	L		E	L		L		V
yellow mombin (f)	Spondias mombin	L	L	H	H		L	L		L	L		L	L	H
yellow mombin (nut)	Spondias mombin	L	L	L	H		L	L		L	L		L	L	H
yellowtaper candletree	Parmentiera aculeata	L	L	V			L	H		L	L		H	L	H
yellow vein (1)	Pseuderanthemum reticulatum		L	H			L	L		L	L		L	H	V
yergan	Cucumeropsis edulis	H	H	H				H		H					
yucca (fl)	Yucca elephantipes	L	L	L	L		L	L		L	L		H	E	V
yucca (sh)	Yucca elephantipes	H	L	H	L		L	L		L	L		H	E	H

[1] d = dry, f = fruit, fl = flower, g = green, 1 = leaf, m = mature, r = root, s = seed, sh = shoot (or bud).

SOURCE: Duke, J. A., "Vegetarian Vitachart, *Quart. J. Crude Drug Res.* 15, 1977, pp. 45-46.

We receive daily inquiries from all over the world asking what herbs are used for what ailments. One Senator asked us for opinions on various quack herbal medicines. Another Senator has shown an interest in the so-called "petroleum nut" *Pittosporum resiniferum* (fig. 10), an energy plant endemic to the Philippines.

Thanks to three professors in the Philippines, we now have seed and a fairly good idea of the ecosystematic amplitudes of the *Pittosporum.* One professor indicated where *Pittosporum resiniferum* was growing prior to widespread relocations in the Philippines for potential energy studies. This information was paired with climate stations in the Climate File to yield ecosystematic amplitudes. Ranging from Tropical Dry to Moist through Subtropical Forest Life Zones, the petroleum nut grows where annual precipitation ranges from 15 to over 50 dm (mean = 27 dm), annual temperature from 18-28° C (mean = 26° C). Of 17 cases where both temperature and rainfall data were available to us, 13 were found in the Tropical Moist Forest Life Zone, three in the Tropical Dry Zone, and one in the Subtropical Rain Forest Life Zone. A similar approach could be used to determine the ecological amplitudes of a medicinal plant, weed, or promising new economic species from the thousands of species **not** among the thousands already in our computer.

Prototypes

We have developed the following three data base prototypes which could be expanded readily if priorities dictated.

Agroforestry File: This program was developed for several species being considered for agroforestry. Different subfiles contain information on eco-

Figure 5.—Ecological Amplitudes of 100 Perennial Weeds

Ecological amplitudes of 100 perennial weeds*

SCIENTIFIC NAME	COMMON NAME	LIFE ZONE	pH	ANN. PRECIP. (DM)	ANN. TEMP. (°C)	WARM WET MONTHS
ACACIA FARNESIANA	HUISACHE	Wd Txm	4.2-8.0	6-40	15-27	0-11
ACER SACCHARUM	SUGAR MAPLE	Cmw Sm	4.5-7.3	5-15	7-21	0-8
ACORUS CALAMUS	SWEETFLAG	Cmw Tvw	5.5-7.5	5-42	7-27	3-12
AGAVE LECHEGUILLA	LECHEGUILLA	Wt Ttv	7.0-7.7	3-6	15-21	2-5
AGROPYRON REPENS	QUACKGRASS	Bmr St	4.2-8.3	3-13	5-23	0-9
AGROSTIS STOLONIFERA	CREEPING BENTGRASS	Bm Wm	4.5-8.3	3-17	6-13	0-6
ALOPECURUS PRATENSIS	MEADOW FOXTAIL	Bw Wt	4.5-7.8	3-17	5-13	0-6
ALYSICARPUS VAGINALIS	ALYCE CLOVER	Sm Tdw	4.3-4.8	10-42	23-29	9-12
AMMOPHILA ARENARIA	EUROPEAN BEACHGRASS	Cmw	4.5-6.2	5-11	7-19	2-6
ANDROPOGON GERARDII	BIG BLUESTEM	Bm Csm	6.3-7.5	5-11	7-27	0-11
ARCTIUM LAPPA	GREAT BURDOCK	Cmw Wtm	4.5-7.8	3-13	6-19	0-6
ARRHENATHERUM ELATIUS	TALL OATGRASS	Bmw Wtm	4.5-8.3	3-16	5-19	0-6
ARTEMISIA ABSINTHIUM	ABSINTH WORMWOOD	Cmw Sd	6.3-8.2	3-13	7-21	0-6
ARUNDO DONAX	GIANT REED	Cw Tdw	5.5-8.3	3-40	9-25	0-11
ATRIPLEX CANESCENS	FOURWING SALTBUSH	Wt	7.3-8.0	3-5	15-19	--
AXONOPUS COMPRESSUS	TROPICAL CARPETGRASS	Sm Tmw	5.8	11-40	19-27	5-12
BOEHMERIA NIVEA	RAMIE	Wdm Tvw	4.3-7.3	7-40	15-27	1-12
BRACHIARIA MUTICA	PARAGRASS	Sdw Tvw	4.3-7.9	8-37	19-27	5-12
BROMUS INERMIS	SMOOTH BROME	Bmw Wtd	5.3-8.2	3-17	5-19	0-5
CALTHA PALUSTRIS	MARSHMARIGOLD	Cmw Wdm	4.8-7.5	4-14	4-17	0-6
CARYA ILLINOENSIS	PECAN	Wtm Sm	5.8-8.3	3-13	13-19	0-7
CASSIA AURICULATA	AVARAM	Sdm Tvw	4.3-7.3	7-42	19-27	5-12
CASTANEA DENTATA	AMERICAN CHESTNUT	Csm Wm	5.8-7.3	5-11	9-15	3-5
CHENOPODIUM AMBROSIOIDES	MEXICANTEA	Cw Tdw	5.5-8.3	3-42	7-27	0-12
CHLORIS GAYANA	RHODESGRASS	Cs Tvw	4.3-8.3	3-40	9-26	0-12
CICHORIUM INTYBUS	CHICORY	Bm Tvm	4.5-8.3	3-40	6-27	0-12
CLITORIA TERNATEA	BLUE PEA	Sdm Tvw	5.8-8.0	7-42	21-29	5-12
COCCOLOBA UVIFERA	SEAGRAPE	Sdm Tvm	5.8-8.0	11-25	21-26	5-12
CORONILLA VARIA	TRAILING CROWNVETCH	Cmw Wdm	5.8-6.8	6-40	7-25	2-11
CORYLUS CORNUTA	BEAKED HAZEL	Bm Cw	5.8-7.5	4-9	6-15	0-5
CYNARA CARDUNCULUS	CARDOON	Cmw Wtm	5.0-8.3	3-12	7-19	0-7
CYNODON DACTYLON	BERMUDAGRASS	Csw Txw	4.3-8.3	3-42	9-29	0-12
CYPERUS ROTUNDUS	PURPLE NUTSEDGE	Bm Txw	4.5-8.3	3-42	6-27	0-12
DACTYLIS GLOMERATA	ORCHARDGRASS	Bmw Sm	4.5-8.3	3-21	5-23	0-9
DICHANTHIUM ANNULATUM	DIAZ BLUESTEM	Sdm Txm	5.7-7.5	2-8	19-25	0-6
DICHONDRA REPENS	DICHONDRA	Wdm Stm	5.0-8.3	3-15	13-23	0-9
DIGITARIA DECUMBENS	PANGOLAGRASS	Sd Tdw	4.3-7.8	9-26	17-27	4-12
DIOSPYROS VIRGINIANA	PERSIMMON	Wdw Sm	5.8-8.0	7-17	15-23	1-9
ECHINOCHLOA CRUSGALLI	BARNYARDGRASS	Bmw Tvw	5.0-8.3	3-23	6-29	0-12
ELEOCHARIS DULCIS	WATERNUT	Sdm Td	5.5-5.7	8-23	19-29	5-10
EQUISETUM ARVENSE	FIELD HORSETAIL	Bmw Tw	4.5-7.5	3-25	6-23	0-9
ERAGROSTIS CURVULA	WEEPING LOVEGRASS	Csw Td	4.3-8.3	3-15	11-23	0-9
FAGUS GRANDIFOLIA	AMERICAN BEECH	Cw Sm	4.5-6.8	9-13	7-19	3-7
FESTUCA ARUNDINACEA	TALL FESCUE	Bmw Sm	4.5-8.5	3-21	5-23	[illegible]
FOENICULUM VULGARE	COMMON FENNEL	Cmw Tvm	5.7-8.3	3-26	4-27	0-12
FRAGARIA VIRGINIANA	VIRGINIA STRAWBERRY	Bmw Sdm	5.3-7.5	4-17	5-23	1-9
GENISTA TINCTORIA	DYERS GREENWOOD	Cmw Wd	4.5-7.5	7-11	9-17	1-6
GENTIANA LUTEA	YELLOW GENTIAN	Cmw Wdm	5.8-6.8	7-11	7-17	1-6
GLYCYRRHIZA GLABRA	COMMON LICORICE	Bm Wt	5.8-8.2	3-7	6-19	0-3
HELIANTHUS TUBEROSUS	JERUSALEM ARTICHOKE	Cmw Tm	4.5-8.3	3-28	7-27	0-12
HORDEUM BULBOSUM	BULBOUS BARLEY	Cs Sd	5.8-8.2	3-9	7-19	0-5
HYPARRHENIA RUFA	JARAGUA GRASS	Sdw Tdw	4.3-6.2	8-40	19-27	4-12
INULA HELENIUM	ELECAMPANE	Cmw Wdm	4.5-7.5	5-13	7-19	1-6
JUGLANS NIGRA	BLACK WALNUT	Cmw Sm	5.8-8.3	3-13	7-19	0-6
JUNIPERUS COMMUNIS	COMMON JUNIPER	Bmw Td	4.5-7.5	4-11	6-21	0-6
LESPEDEZA STRIATA	JAPANESE LESPEDEZA	Wdm Sm	5.0-8.8	5-17	9-23	3-9
LESQUERELLA GORDONII	GORDON BLADDERPOD	Wt	7.3-7.8	3-9	15	--

*For explanation see text.

SOURCE: Duke, J. A., "Perennial Weeds as Indicators of Annual Climatic Parameters," *Agricultural Meteorology*, 16:291-294, (Amsterdam: Elsevier Scientific Publishing Co., 1976).

Figure 6.—Proximate Analysis

16:55 THURSDAY, SEPTEMBER 30, 1902

PLCO	VARNT	REFCO	PARTCODE	CALORIES	WATER	PROTEIN	FAT	CARBO	FIBER	ASH	CALCIUM
000001001 Equisetum arvense		2	L	20	93.7000	1	0.200000	4.40000	1.10000	0.700000	58

PLCO	PHOSPHO	IRON	SODIUM	POTASS	CAROT	THIAMINE	ASCORBIC	NIACIN	RIBOFLAV
000001001	93	4.40000	.	.	300	0	50	5.60000	0.0700000

ZERO MOISTURE

(all values except water multiplied by $\frac{100}{100-\underline{x}}$ where $\underline{x}$ = % H_2O)

PLCO	VARNT	REFCO	PARTCODE	CALORIES	WATER	PROTEIN	FAT	CARBO	FIBER	ASH	CALCIUM
000001001 Equisetum arvense		2	L	317.460	0	15.8730	3.17460	69.8413	17.4603	11.1111	920.635

PLCO	PHOSPHO	IRON	SODIUM	POTASS	CAROT	THIAMINE	ASCORBIC	RIBOFLAV	NIACIN
000001001	1476.19	69.8413	.	.	4761.90	0	793.651	1.11111	88.8889

SOURCE: *Nutrition*, PLCO Economic Botany Laboratory.

Figure 7.—Pertinent Pages From Phytotoxin Tables

Toxins: Their Toxicity and Distribution in Plant Genera

Chemical	Toxicity[a,b]	Plant genera
Quinaldine	orl rat LD_{50}, 1,230 mg skn rbt LD_{50}, 1,870 mg	*Galipea*
Quinazoline	skn mus TDLo, 4,000 mg/Y1 NEO	*Dichroa*?
Quinic acid	scu mus LD_{50}, 10,000 mg	*Aconitum, Angelica, Arctostaphylos, Cinchona, Daucus, Eucalyptus, Illicium, Linum, Malus, Medicago, Nicotiana, Pistacia, Prunus, Rosa, Terminalia, Vaccinium*
Quinidine	orl rat LD_{50}, 1,000 mg orl mus LD_{50}, 594 mg ipr rat LDLo, 174 mg ipr mus LD_{50}, 190 mg	*Cinchona, Coutarea, Enantia, Remijia, Strychnos*
Quinine	orl wmn TDLo, 20 mg (4–5 W preg) TER orl rbt LDLo, 800 mg orl gpg LDLo, 300 mg unk gpg TDLo, 200 mg preg TER	*Cinchona, Cornus, Coutarea, Enantia, Ladenbergia, Picrolemma, Remijia, Strychnos*
Quinoline	orl rat LD_{50}, 460 mg ipr mus LDLo, 64 mg skn rbt LD_{50}, 540 mg	*Citrus*
Raton	scu rat TDLo, 31 g/61 W1 NEO	*Gliricidia*
Red squill	orl rat LD_{50}, 200 mg	*Scilla*
Red thyme oil	orl rat LD_{50}, 4,700 mg	*Thymus*
Rescinnamine	orl mus LD_{50}, 1,420 mg	*Rauwolfia, Tonduzia*
Reserpine	orl hmn TDLo, 14 µg PSY ims hmn TDLo, 357 µg PSY unk rat TDLo, 1,500 µg (9–10 D preg) TER	*Alstonia, Aspidosperma, Bleekeria, Excavatia, Ochrosia, Rauwolfia, Tonduzia, Vallesia, Vinca, Voacanga*
Retronecine	ivn rat LD_{50}, 1,311 mg ivn mus LD_{50}, 634 mg	Usually combined. *Amsinckia, Brachyglottis, Crotalaria, Echium, Emilia, Erechtites, Heliotropium, Petasites, Senecio, Trichodesma, Tussilago*
Retinol	orl rat TDLo, 55 mg	Widespread?

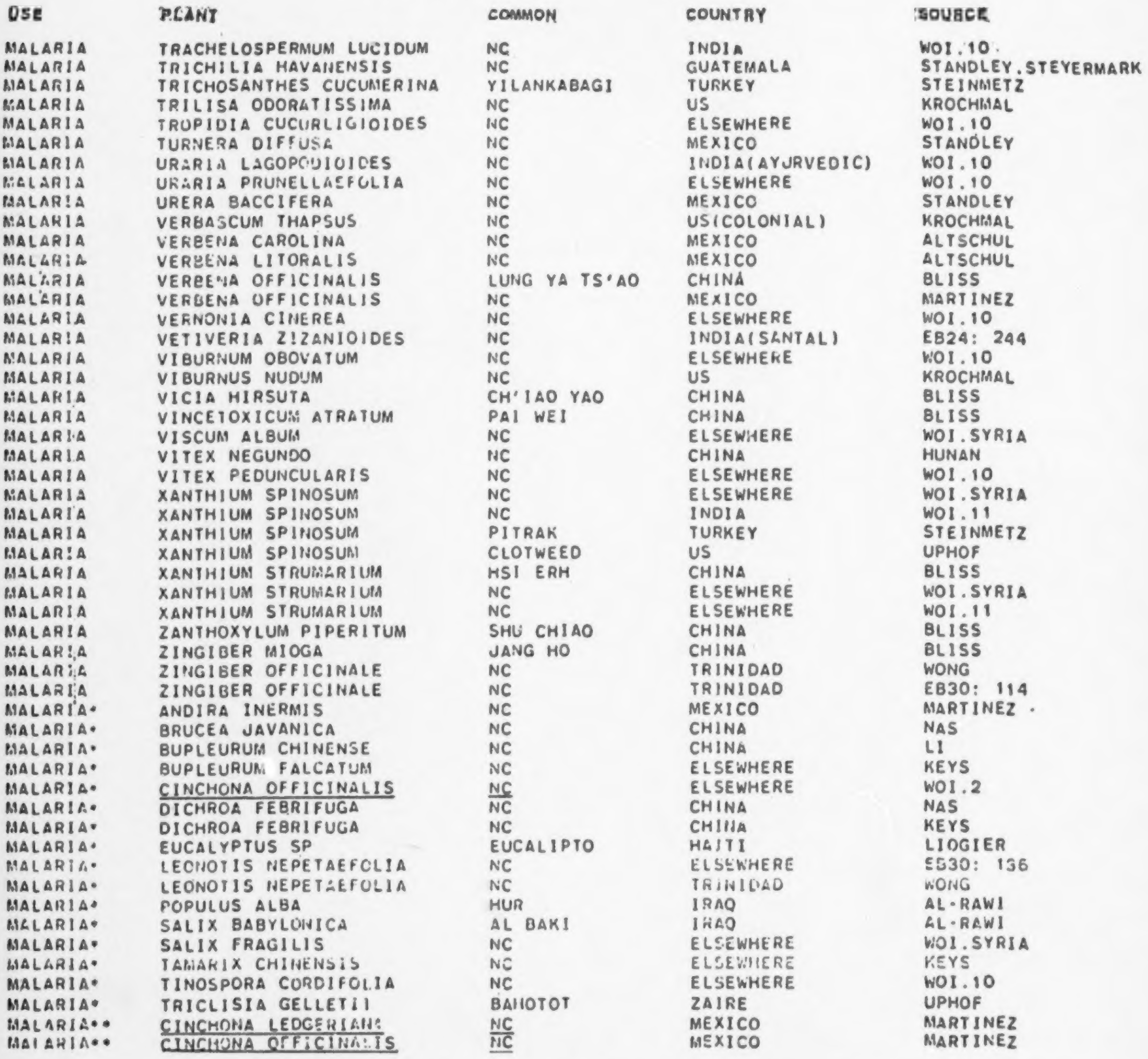
TABLE 2 (continued)

Higher Plant Genera and Their Toxins

Genus[a]	Family	Toxin
Cinchona	Rubiaceae	Cinchonidine, cinchonine, quinic acid, quinidine, quinine, saponin
Cinnamomum	Lauraceae	Acetaldehyde, benzoic acid, borneol, caproic acid, caprylic acid, carvacrol, cassia oil, cineole, cinnamaldehyde, cinnamyl alcohol, citronellol, coumarin, cuminic alcohol, cuminic aldehyde, cymene, decanal, eugenol, eugenol methyl ether, formic acid, furfural, geraniol, hydrocyanic acid, isobutyric acid, isoeugenol, isovaleraldehyde, isovaleric acid, lauric acid, limonene, linalool, myristic acid, myristicin, nonlyl alcohol, phellandrene, piperonal, propionic acid, safrole, salicylaldehyde, salicylic acid, shikimic acid, tannic acid, terpineol
Cirsium[b]	Asteraceae	Hydrocyanic acid
Cissus[b]	Vitaceae	Hydrocyanic acid
Cistus	Cistaceae	Acetophenone, formic acid

SOURCE: Duke, J. A., "Phytotoxin Tables," *CRS Critical Reviews in Toxicology* 5(3): 189-237, 1977.

Figure 8.—Sample Ethnomed Printout



USE	PLANT	COMMON	COUNTRY	SOURCE
MALARIA	TRACHELOSPERMUM LUCIDUM	NC	INDIA	WOI.10
MALARIA	TRICHILIA HAVANENSIS	NC	GUATEMALA	STANDLEY.STEYERMARK
MALARIA	TRICHOSANTHES CUCUMERINA	YILANKABAGI	TURKEY	STEINMETZ
MALARIA	TRILISA ODORATISSIMA	NC	US	KROCHMAL
MALARIA	TROPIDIA CUCURLIGIOIDES	NC	ELSEWHERE	WOI.10
MALARIA	TURNERA DIFFUSA	NC	MEXICO	STANDLEY
MALARIA	URARIA LAGOPODIOIDES	NC	INDIA(AYURVEDIC)	WOI.10
MALARIA	URARIA PRUNELLAEFOLIA	NC	ELSEWHERE	WOI.10
MALARIA	URERA BACCIFERA	NC	MEXICO	STANDLEY
MALARIA	VERBASCUM THAPSUS	NC	US(COLONIAL)	KROCHMAL
MALARIA	VERBENA CAROLINA	NC	MEXICO	ALTSCHUL
MALARIA	VERBENA LITORALIS	NC	MEXICO	ALTSCHUL
MALARIA	VERBENA OFFICINALIS	LUNG YA TS'AO	CHINA	BLISS
MALARIA	VERBENA OFFICINALIS	NC	MEXICO	MARTINEZ
MALARIA	VERNONIA CINEREA	NC	ELSEWHERE	WOI.10
MALARIA	VETIVERIA ZIZANIOIDES	NC	INDIA(SANTAL)	EB24: 244
MALARIA	VIBURNUM OBOVATUM	NC	ELSEWHERE	WOI.10
MALARIA	VIBURNUS NUDUM	NC	US	KROCHMAL
MALARIA	VICIA HIRSUTA	CH'IAO YAO	CHINA	BLISS
MALARIA	VINCETOXICUM ATRATUM	PAI WEI	CHINA	BLISS
MALARIA	VISCUM ALBUM	NC	ELSEWHERE	WOI.SYRIA
MALARIA	VITEX NEGUNDO	NC	CHINA	HUNAN
MALARIA	VITEX PEDUNCULARIS	NC	ELSEWHERE	WOI.10
MALARIA	XANTHIUM SPINOSUM	NC	ELSEWHERE	WOI.SYRIA
MALARIA	XANTHIUM SPINOSUM	NC	INDIA	WOI.11
MALARIA	XANTHIUM SPINOSUM	PITRAK	TURKEY	STEINMETZ
MALARIA	XANTHIUM SPINOSUM	CLOTWEED	US	UPHOF
MALARIA	XANTHIUM STRUMARIUM	HSI ERH	CHINA	BLISS
MALARIA	XANTHIUM STRUMARIUM	NC	ELSEWHERE	WOI.SYRIA
MALARIA	XANTHIUM STRUMARIUM	NC	ELSEWHERE	WOI.11
MALARIA	ZANTHOXYLUM PIPERITUM	SHU CHIAO	CHINA	BLISS
MALARIA	ZINGIBER MIOGA	JANG HO	CHINA	BLISS
MALARIA	ZINGIBER OFFICINALE	NC	TRINIDAD	WONG
MALARIA	ZINGIBER OFFICINALE	NC	TRINIDAD	EB30: 114
MALARIA*	ANDIRA INERMIS	NC	MEXICO	MARTINEZ
MALARIA*	BRUCEA JAVANICA	NC	CHINA	NAS
MALARIA*	BUPLEURUM CHINENSE	NC	CHINA	LI
MALARIA*	BUPLEURUM FALCATUM	NC	ELSEWHERE	KEYS
MALARIA*	CINCHONA OFFICINALIS	NC	ELSEWHERE	WOI.2
MALARIA*	DICHROA FEBRIFUGA	NC	CHINA	NAS
MALARIA*	DICHROA FEBRIFUGA	NC	CHINA	KEYS
MALARIA*	EUCALYPTUS SP	EUCALIPTO	HAITI	LIOGIER
MALARIA*	LEONOTIS NEPETAEFOLIA	NC	ELSEWHERE	EB30: 136
MALARIA*	LEONOTIS NEPETAEFOLIA	NC	TRINIDAD	WONG
MALARIA*	POPULUS ALBA	HUR	IRAQ	AL-RAWI
MALARIA*	SALIX BABYLONICA	AL BAKI	IRAQ	AL-RAWI
MALARIA*	SALIX FRAGILIS	NC	ELSEWHERE	WOI.SYRIA
MALARIA*	TAMARIX CHINENSIS	NC	ELSEWHERE	KEYS
MALARIA*	TINOSPORA CORDIFOLIA	NC	ELSEWHERE	WOI.10
MALARIA*	TRICLISIA GELLETII	BANOTOT	ZAIRE	UPHOF
MALARIA**	CINCHONA LEDGERIANA	NC	MEXICO	MARTINEZ
MALARIA**	CINCHONA OFFICINALIS	NC	MEXICO	MARTINEZ

SOURCE: Duke, J. A., and Wain, K. K., "Medicinal Plants of the World," computer index with more than 85,000 entries, 3 vols., 1981.

Figure 9.—Sample of Insecticide Subset of ETHNOMED

USE	PLANT	COMMON	COUNTRY	SOURCE
INSECTICIDE	ZANTHOXYLUM ARMATUM	NC	ELSEWHERE	WOI.11
INSECTICIDE	ZANTHOXYLUM NITIDUM	NC	ELSEWHERE	WOI.11
INSECTICIDE(VET)	DELPHINIUM BRUNONIANUM	NC	ELSEWHERE	UPHOF
INSECTICIDE(VET)	GARDENIA LUCIDA	NC	ELSEWHERE	UPHOF
INSECTICIDE*	ACORUS CALAMUS	NC	ELSEWHERE	WOI.1
INSECTICIDE*	ADHATODA VASICA	NC	INDIA	WOI.SYRIA
INSECTICIDE*	ANNONA CHERIMOLA	CHERIMOYA	LA	LEWIS
INSECTICIDE*	CINCHONA OFFICINALIS	NC	ELSEWHERE	WOI.2
INSECTICIDE*	ECLIPTA ALBA	NC	ELSEWHERE	NAS
INSECTICIDE*	GALPHIMIA GLAUCA	NC	NL	LEWIS
INSECTICIDE*	GYNOCARDIA ODORATA	NC	INDIA	WOI.4
INSECTICIDE*	MAMMEA AMERICANA	NC	ELSEWHERE	EB30: 132
INSECTICIDE*	MAMMEA AMERICANA	MAMEY	LA	LEWIS
INSECTICIDE*	MAMMEA AMERICANA	NC	TRINIDAD	WONG
INSECTICIDE*	NERIUM INDICUM	NC	INDIA	WOI.7
INSECTICIDE*	OCIMUM BASILICUM	NC	ELSEWHERE	WOI.SYRIA
INSECTICIDE*	OCIMUM SANCTUM	NC	ELSEWHERE	WOI.7
INSECTICIDE*	PACHYRRHIZUS EROSUS	YAMBEAN	LA	LEWIS
INSECTICIDE*	PHELLODENDRON AMURENSE	NC	ELSEWHERE	NAS
INSECTICIDE*	PICRASMA EXCELSA	NC	ELSEWHERE	WOI.8
INSECTICIDE*	PIMPINELLA ANISUM	NC	ELSEWHERE	WOI.SYRIA
INSECTICIDE*	PISCIDIA PISCIPULA	NC	ELSEWHERE	WOI.8
INSECTICIDE*	PSEUDOTSUGA MENZIESII	NC	ELSEWHERE	WOI.8
INSECTICIDE*	QUASSIA AMARA	NC	ELSEWHERE	WOI.8
INSECTICIDE*	RYANIA SPECIOSA	NC	ELSEWHERE	EB26: 233
INSECTICIDE*	SALVIA OFFICINALIS	NC	ELSEWHERE	WOI.SYRIA
INSECTICIDE*	SAUSSUREA LAPPA	NC	CHINA	NAS
INSECTICIDE*	SOPHORA TOMENTOSA	NC	ELSEWHERE	WOI.9
INSECTICIDE*	SPHAERANTHUS AFRICANUS	NC	ELSEWHERE	WOI.10
INSECTICIDE*	SPILANTHES ACMELLA	NC	ELSEWHERE	WOI.10
INSECTICIDE*	SPILANTHES OLERACEA	NC	ELSEWHERE	WOI.10
INSECTICIDE*	TAGETES PATULA	NC	ELSEWHERE	WOI.10
INSECTICIDE*	TEPHROSIA BRACTEOLATA	NC	INDIA	WOI.10
INSECTICIDE*	TEPHROSIA CANDIDA	NC	INDIA	WOI.10
INSECTICIDE*	TEPHROSIA NOCTIFLORA	NC	INDIA	WOI.10
INSECTICIDE*	TEPHROSIA PROCUMBENS	NC	INDIA	WOI.10
INSECTICIDE*	TEPHROSIA VOGELII	NC	INDIA	WOI.10
INSECTICIDE*	TRACHYSPERMUM AMMI	NC	ELSEWHERE	WOI.SYRIA
INSECTICIDE*	TRIANTHEMA PORTULACASTRUM	NC	ELSEWHERE	WOI.10
INSECTICIDE*	TRICHODESMA ZEYLANICUM	NC	ELSEWHERE	WOI.10
INSECTICIDE*	VERATRUM VIRIDE	NC	US	WOI.10
INSECTICIDE*	ZANTHOXYLUM OXYPHYLLUM	NC	ELSEWHERE	WOI.11
INSECTICIDE**	DERRIS ELLIPTICA	NC	INDIA	WOI.3
INSECTICIDE**	DERRIS FERRUGINEA	NC	INDIA	WOI.3
INSECTICIDE**	DERRIS MALACCENSIS	NC	ELSEWHERE	WOI.3
INSECTICIDE**	DERRIS ROBUSTA	NC	ELSEWHERE	WOI.3
INSECTICIDE**	EUCHRESTA HORSFIELDII	NC	INDIA	WOI.3
INSECTICIDE**	HURA CREPITANS	NC	ELSEWHERE	WOI.5
INSECTICIDE**	MAMMEA AMERICANA	NC	ELSEWHERE	WOI.6
INSECTICIDE**	MELIA TOOSENDAN	NC	CHINA	LI
INSECTICIDE**	SPERGULA ARVENSIS	NC	ELSEWHERE	WOI.SYRIA
INSECTIFUGE*	CARAPA GUIANENSIS	NC	ELSEWHERE	EB30: 127

SOURCE: Duke, J. A., and Wain, K. K., "Medicinal Plants of the World," computer index with more than 85,000 entries, 3 vols., 1981.

Figure 10.—*Pittosporum resiniferum*

SOURCE: ©Peggy Duke.

logical parameters, germination requirements, nutrition values, cultural requirements, yields, wood characteristics, use, and plant pathology. A sample of the Agroforestry File is given in figure 11. Perhaps the greatest impact of the prototype was to show that almost no data were available on most nonconventional economic plants. The Agroforestry File is most applicable to Third World countries.

Pest File: This prototype has only about 2,500 entries. It lists the scientific name of the host plant, the plant part affected by the disease or the insect, and the name and type of pest. The scientific name enables this file to communicate with any other file, such as the Agroforestry File (fig. 11).

Our ecosystematic file has helped locate herbs important to nematode taxonomy. Nematodes should be included in any pest prototype. Several years ago, Russian workers reported a most unusual nematode from a limited area of Russia on *Mentha longifolia.* Soon afterwards Dr. Morgan Golden found a nematode similar to *Meloidoderita kirjunovae,* the Russian species, on a polygonum at Beltsville. Without Russian specimens or a better description of *M. kirjunovae,* it was impossible to make a final identification of the Beltsville specimen. After testing true *Mentha longifolia* with this *Melodidoderita* specimen, Golden found that his nematode did not attack *M. longifolia,* the type host for the Russian nematode. With this information and further morphological study, Golden proved that the Beltsville specimen represented an undescribed *Meloidoderita* species. Without testing with *Mentha,* the identification and classification of the *Meloidoderita* would have been much less conclusive.

For years I have campaigned for a program that would record the ecological amplitudes of pests and diseases as we have done with economic plants and weeds. Knowledge of the ecological amplitudes of crops and their pests could launch a new phase in biological control of pests' "biological evasion" (4). Where the host tolerates more cold than the pests, planting in the colder area might be advantageous. For example, in Chowan County, N.C., near the northern limits of the cotton plant and the boll weevil, the cotton grows well but the weevil does not. This lack of crop and pest overlap may be used to good advantage by the USDA (2).

Intercropping: Because of our involvement with the Agroforestry project, we had a greater interest in intercropping than most conventional farming units in the USDA. My colleague at USDA, Dr. Atchley, set up a prototype Intercropping file. Now on tape but not on-line, it lists major and minor crop combinations, all species in pasture mixes, yield data, yield differentials, cultural variables, etc. Using the scientific names to link this and other files, one could find out which crops have been tried around the world as intercrops. In densely populated Third World areas, intercropping clearly promises more quality, quantity, and/or variety of crops per hectare than monocropping.

Limitations

In intermediate ecotypes, the effects of factors such as slope, soil porosity, soil type, vegetation cover, cultural conditions, insolation, prevailing winds, etc. on plant characteristics may be significant. Few data are available and we have entered some of these variables for only a few places. This is a major limitation of our program.

Figure 11.—Agroforestry Pest File

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                       PLANTS THAT ARE POTENTIAL FUEL SOURCES
                    COMPUTERIZED BY THE ECONOMIC BOTANY LABORATORY
                        ALAN A. ATCHLEY AND ERIC S. MATHIS

           PLNA                PLCO      AUTHOR           VALID PEST                                PESTTYPE PARTAFEC BIOCNTL CODE

EUCALYPTUS CAMALDULENSIS  453046001 SCHLECHT.           N   TRICENTA ARGENTATA                      I      WS             114
EUCALYPTUS CITRIODORA     453046003 HOOK.                   TRAMETES CUBENSIS                       F      HEA            000
EUCALYPTUS GLOBULUS       453046004 LABILL.                 FUNGUS                                  F                     114
EUCALYPTUS GLOBULUS       453046004 LABILL.                 MOTH                                    I                     114
EUCALYPTUS GLOBULUS       453046004 LABILL.                 PSYLLID                                 I                     114
EUCALYPTUS GLOBULUS       453046004 LABILL.                 SCALE                                   I                     114
EUCALYPTUS GLOBULUS       453046004 LABILL.                 SNOUT BEETLE                            I                     114
EUCALYPTUS GLOBULUS       453046004 LABILL.
EUCALYPTUS GOMPHOCEPHALA  453046005 DC.
EUCALYPTUS GRANDIS        453046002                         PAROPSIS DILATATA                       I      BK             114
EUCALYPTUS GRANDIS        453046002                         CHRYSOPHTHARTA SP.                      I      BK             114
EUCALYPTUS MARGINATA      453046010 SM.                     BORERS                                  I                     114
EUCALYPTUS MARGINATA      453046010 SM.                     MOTHS                                   I                     114
EUCALYPTUS MARGINATA      453046010 SM.                     TERMITES                                I                     114
EUCALYPTUS MICROTHECA     453046006 F.MUELL.
EUCALYPTUS OCCIDENTALIS   453046007 ENDL.
EUCALYPTUS SP.            453046000                     Y   283016001
EUCALYPTUS TERETICORNIS   453046006 SM.
GLEDITSIA TRIACANTHOS     283110002
GLIRICIDIA SEPIUM         283300001 (JACQ.) STEUD.          PSEUDOCOCCUS VIRGATUS                   I                     102
GMELINA ARBOREA           533056001 ROXB.
GREVILLEA ROBUSTA         129030001 A. CUNN.            N
GUAZUMA ULMIFOLIA         380026001 L.
HALOXYLON PERSICUM        150057002 BUNGE EX BOISS.
INGA BOURGONI             283002006 SCOP.
INGA SP.                  283002000
INGA URAGUENSIS           283002007 HOOK.&ARN.
INGA VERA                 283002003 WILLD.              N
LESPEDEZA BICOLOR         283386004
LESPEDEZA CAPITATA        283386005
LESPEDEZA CUNEATA         283386001
LESPEDEZA CYRTOBOTRYA     283386006
LESPEDEZA HIRTA           283386013
LESPEDEZA HOMOLOBA        283386007
LESPEDEZA PILOSA          283386009
LESPEDEZA PROCUMBENS      283386014
LESPEDEZA REPENS          283386015
LESPEDEZA SP.             283386000
LESPEDEZA STIPULACEA      283386002
LESPEDEZA STRIATA         283386003
LEUCAENA LEUCOCEPHALA     283013001 (LAM.) DE WIT           SEED WEEVIL                             I      FR             119
LEUCAENA LEUCOCEPHALA     283013001 (LAM.) DE WIT           TWIG BORERS                             I      TW             119
LEUCAENA LEUCOCEPHALA     283013001 (LAM.) DE WIT           TERMITES                                I                     119
LEUCAENA LEUCOCEPHALA     283013001 (LAM.) DE WIT           FUNGUS                                  F      SD             119
LEUCAENA LEUCOCEPHALA     283013001 (LAM.) DE WIT           WEEVILS                                 I                     000
LEUCAENA LEUCOCEPHALA     283013001 (LAM.) DE WIT           FUSARIUM SOLANI(E.&G.MART.)JONES&GROUT                        137
MELIA AZEDARACH           312021001 L.
MIMOSA SCABRELLA          283015013 BENTH.
MUNTINGIA CALABURA        371008001 L.
PHYLLANTHUS EMBLICA       328014002                         RAVENELIA EMBLICAE                      F               000   263117
PITHECELLOBIUM DULCE      283007003 (ROXB.) BENTH.          PHYLLOSTICTA INGRA-DULCIS               F      LF             102
PITHECELLOBIUM DULCE      283007003 (ROXB.) BENTH.          COLLETOTRICUM SPP.                      F      LF             102
PITHECELLOBIUM DULCE      283007003 (ROXB.) BENTH.          BORING INSECTS                          I                     102
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SOURCE: Economic Botany Laboratory.

We need to get soil taxonomic units from a unified soil classification system for all 20,000 locales for which we have climatic data. This would require a major cooperative venture. Much more of the world is mapped in the FAO system than in the USDA Soil Conservation Service's Soil Taxonomy. The Benchmark program is using the USDA rather than the FAO system for site management.

There is a tendency of some soil scientists to assert that soil is THE determinant in the distribution and yield of economic plants, of some climatologists to believe the climate is the determinant, and of some plant ecologists to believe the vegetation type is the determinant. I suspect that all plant distributions are determined by interaction of all three and other factors as well. Unfortunately, the computer cannot identify the most important factors affecting a given species. For some species, vegetation will be the most definitive determinant; for others, soil; for others, climate. We need a major program to collate the FAO and/or USDA soil units with the 20,000 climatic data sites, soil pH, weeds, crops, yields, diseases, insect pests, native perennials, etc. This should be done for a sufficiently large number of the 20,000 sites to develop ecological (including both climatological and pedological data) amplitudes and means and determine optimal conditions for all the economic species of the world and their pests and pathogens. This system, which could be called the International Plant Utilization Data Base (IPUD), would answer a multitide of questions and avoid many costly problems.

For example, with this one-time multimillion dollar project, one could prevent many multimillion dollar mistakes made in introducing the wrong species in developing countries. It could help developing countries develop import substitution programs which might save them million of dollars. This might make the country more self-sufficient and decrease its need for transporting goods.

The perennials growing in remote areas can help one assess the plants best grown there. The IPUD could help one map the areas in a country where a plant introduction is most likely and least likely to succeed. Ancillary to this should be the development of an economic data base (such as is hinted at in fig. 12), which includes transportation costs, shelf life, world demand, trends in production, and current price of a species. Crops that make the most sense economically then could be chosen from the many crops ecologically adapted to the remote area. All should be tried experimentally before planted on a large scale. Experimental data resulting from trials would be used to select the right species for that particular area and to augment and refine the data base.

We have developed several prototype files that could attack big problems systematically. Currently these files are undersupported; we have not yet convinced international authorities of the value of an International Plant Utilization Data Base. Such a data base could reduce international agricultural trade while improving internal trade deficits accordingly. It could reduce the petroleum used in international transport of agricultural goods. The IPUD could select species best adapted to a given climate for whole-plant utilization schemes in which food, oilseeds, leaf-proteins, chemurgics, drugs, etc. would be the main products and biomass would be an energy-producing or commercial fiber byproduct. Greater plant use becomes more important as petroleum supplies become more scarce and expensive.

Implications

Without funding, our data bases now have a life expectancy of no more than 3 years. The cost of maintaining our files online is more than $10,000 a year, even before any programs are run on the data. Are they worth the cost? Who can use them? The data bases' contribution to the quest for sorghum tolerant of high alkali soils, a multimillion dollar problem, already has been cited. Similar searches for germ plasm suitable to marginal environments might be made for any of the hundreds of economic species and thousands of medicinal species. USDA is a constant user; daily it consults the hard copy generated by the EBL data base to answer questions on agronomy, agroforestry, climate, ecology, ethnomedicine, nutrition, pathology, and utilization.

Many other agencies have benefitted from the files and could reduce future costs by consulting them. Some examples are given below.

Agency	*Questions We Can Help Answer*	*File(s)*
AID	What crops are best adapted to Lesotho?	ECOSYSTEMAT
	What trees can you recommend for reforestation in Haiti?	AGROFOREST
	USDA, in colloboration with NAS and NIFTAL, is setting up some provenance trials. What species would you suggest?	ECOSYSTEMAT
APHIS	Where in the U.S. is niger seed, an ingredient of birdseed, most likely to become a weed?	ECOSYSTEMAT
	Which of the Chinese medicinal plants—e.g., honeysuckle, kudzu, and perilla—are most liable to become weeds around the various ports of entry?	ECOSYSTEMAT CHINA CLIMATE
CIA	Where in South America can *Erythroxylum* be grown?	CLIMATE ECOSYSTEMAT

	Do the trees in the background behind these maneuvers indicate that this is a tropical, temperate, or subarctic area?	CLIMATE ECOSYSTEMAT
	What trichothecene-like compounds are produced by species tolerant of the Laotian climate?	CLIMATE
DOD	If our supplies of atropine were cut off, what would be the best places in the United States to grow the various species that contain atropine?	PHYTOTOXIN
	Give us addresses of seed sources from our allies.	ECOSYSTEMAT CLIMATE
	Which herbs grown in Teheran are good sources of vitamin C?	NUTRITION
	List the edible and medical species of Iran.	GEOGRAPHY UTILIZAT
DOE	What phytomass yields have been reported from Panama? What species is the highest biomass producer reported in your file? What is the standing biomass of the Republic of Panama?	PHYTOMASS YIELDS
	List the major crops and energy potential of their residue for 66 developing countries.	ECOSYSTEMAT PHYTOMASS YIELDS
FDA	What species contain safrole?	PHYTOTOXIN
	We need 100 lb of comfrey root from different latitudes to check out variability in carcinogenicity.	ECOSYSTEMAT
NAS	What is the nutritional value of the neglected legume species of the world?	NUTRITION
NIDA	Assuming Bolivia, Colombia, and Peru all phase out coca, where else in Latin America can it best be grown? What about *Cannabis*? *Papaver somniferum*? What tree crops can be grown around Chipiriri, Bolivia, where cocaine production is being discouraged? What herbs can be grown in the Golden Triangle where they are phasing out poppy production?	
	What crops can be grown in the peat swamps of Jamaica, where the ganja is being grown?	ECOSYSTEMAT CLIMATE
NIFTAL	What legumes, other than caesalpinoid legumes, can you recommend for tropical moist forest, elfin forest, subtropical thorn forest, and warm temperate rain forest?	ECOSYSTEMAT CLIMATE
	What are the medicinal uses of our 44 major nitrogen-fixing species?	ETHNOMED
NIH	Where can we get several tons of winged bean?	ECOSYSTEMAT
	What are the folk anticancer plants of China?	ETHNOMED
NIOSH	What carcinogenic compounds are found in the herbs and spices processed here in the United States?	PHYTOTOXIN
OTA	List in order of decreasing protein content the top 100 leaf-protein producers on a zero-moisture basis.	NUTRITION
	Which would do best in the tobacco belt of the Carolinas? Which species could give the most leaf protein per hectare?	YIELDS
SBA	What commercial crops can you recommend for the Lake Miragone region of Haiti?	CLIMATE ECOSYSTMAT
VITA	What firewood trees can you recommend for our site in Ecuador, with a climate identical with that in Quito?	AGROFOREST CLIMATE
	What natural pesticide species—such as neem, pyrethrum, and ryania—can you recommend for the San Jose area of Costa Rica?	ETHNOMED
	What living-fence post trees produce the best firewood for Columbia?	AGROFOREST CLIMATE
VISTA	What esoteric culinary herbs can you recommend for the climate in Oregon?	ETHNOMED
WHO	List contraceptive plants. List molluscicidal plants.	ETHNOMED
WRAR	What are the medicinal uses of *Polygonum alpinum*?	ETHNOMED
	What antimalarial species grow in Nigeria?	ETHNOMED

AID — Agency for International Development
APHIS — Animal and Plant Health Inspection Service
CIA — Central Intelligence Agency
DOD — Department of Defense
DOE — Department of Energy
FDA — Food and Drug Administration
NAS — National Academy of Sciences
NIDA — National Institute of Drug Abuse
NIFTAL — Nitrogen Fixation By Tropical Agricultural Legumes
NIH — National Institute of Health
NIOSH — National Institute of Occupational Safety and Health
OTA — Office of Technology Assessment
SBA — Small Business Administration
VITA — Volunteers in Technical Assistance
VISTA — Volunteers in Service to America
WHO — World Health Organization
WRAR — Walter Reed Army Research

There are partial or complete answers to these questions in the files of the data base, now off-line. These are samples representing only a few of the innumerable possible questions, many of which have not even been asked, much less answered. The development and maintenance of an International Plant Utilization Data Base, an on-line interlocking system with agronomic, biochemical, climatological, ecological, economic, entomological, geographic, pathological, pedological, and use data on the thousands of economic plant species, could help answer present and future questions.

Appendix I: Latin American Localities Suitable for Date Palm Cultivation

by Alan A. Atchley*

"The date palm must have its feet in water and its head in fire," goes an old Arab saying. The familiar image of a desert oasis supporting a grove of these palms surrounded by barren dunes seems to fulfill this proverb, for the trees are "naturally irrigated" by the waters of the oasis and their crowns are exposed to some of the hottest weather in the world. But the oasis draws its water from the natural rainfall over a wide expense, and the palms are not independent of the rainfall component of the climate as they would be under artificial irrigation.

Can modern data processing techniques reveal the climatic tolerances of this important palm species and suggest where it might be introduced successfully? The Economic Botany Laboratory's methods were applied to find sites in Latin America where, based on the computerized information in AEGIS (Agricultural, Ecological, Geographic Information System), date palms might grow successfully. (AEGIS is handled with the SAS programing

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Figure 12.—Sample Page From Botanical Price Lists

Abies siberica oil	$	8.50 -	9.00/lb
Allspice	$	1.02 -	1.19/lb
Allyl isothiocyanate	$	7.25 -	7.80/lb
Almond oil	$	1.20 -	4.00/lb
Aloe	$	.61 -	1.50/lb
Aloin	$	5.75 -	6.00/lb
Amyris	$	-	9.50/lb
Anethole	$	-	2.50/lb
Angelica root oil	$	-	800.00/lb
Anise oil	$	11.50 -	13.00/lb
Anise seed	$	1.40 -	1.60/lb
Apricot kernel oil	$	-	2.00/lb
Arabic gum	$	.89 -	1.44/lb
Avocado oil	$	4.00 -	4.85/lb
Bay oil	$	10.75 -	12.50/lb
Bayberry wax	$	2.70 -	3.00/lb
Belladonna leaf	$	2.40 -	2.45/lb
Benzaldehyde	$	1.24 -	1.28/lb
Caffeine	$	-	4.80/lb
Calamus oil	$	-	55.00/lb
Camphor	$	3.63 -	3.70/lb
Camphor oil	$	1.00 -	2.25/lb
Cananga oil	$	22.00 -	23.00/lb
Candelilla wax	$	1.90 -	2.10/lb
Capsicum oleoresin	$	8.40 -	16.50/lb
Caraway oil	$	29.00 -	30.00/lb
Caraway seed	$	.55 -	.69/lb
Cardamon	$	3.00 -	4.50/lb
Carnauba wax	$	1.10 -	2.05/lb
d-Carvone	$	-	48.00/lb
l-Carvone	$	8.50 -	9.75/lb
Cascara sagrada	$	-	1.0[illegible]/lb
Cassia	$	.67 -	.80/lb
Castor oil	$	.46 -	.68/lb
Castor pomace	$	-	135.50/ton
Catechol	$	2.94 -	7.48/kilo
Cedarleaf oil	$	1.90 -	2.10/lb
Cedarwood oil	$	2.35 -	3.00/lb
Celery seed	$	.46 -	.47/lb
Celery seed oil	$	29.50 -	45.35/lb
Chamomile flowers	$	3.35 -	4.94/lb
Chamomile oil	$	-	370.90/lb
Chenopodium oil	$	-	11.00/lb
Cherry kernel oil	$	1.00 -	1.40/lb
Cinnamon	$	.50 -	1.35/lb
Cinnamon bark oil	$	240.00 -	250.00/kilo
Cinnamon leaf oil	$	2.90 -	3.00/lb
Citral, Natural	$		6.25/lb
Citronella oil, Ceylon	$	2.20 -	2.60/lb
Citronella oil, Java	$	3.45 -	4.75/lb
Citronella oil, China	$	-	8.75/lb
Citronellal	$	4.00 -	6.20/lb
Citronellol	$	4.90 -	10.00/lb
Clove leaf oil	$	1.95 -	4.00/lb
Clove bud oil	$	19.50 -	28.00/lb
Cloves	$	5.00 -	5.10/lb
Cocaine hydrochloride	$		-900.00/kilo
Cocillana bark	$	.40 -	.45/lb
Codeine	$		-900.00/kilo
Coriander oil	$	25.00 -	37.00/lb
Coriander seed	$	.34 -	.41/lb
Corn oil	$	.13½-	.14/lb
Cottonseed oil	$	-	.13/lb
Coumarin	$	-	6.20/lb
Cube root	$	-	.60/lb
Cumene	$	-	.23½/lb
Cumin seed	$	-	1.03/lb
Cyclamen aldehyde	$	-	6.00/lb
Digitoxin	$	2.60 -	3.00/gram
Dillweed oil	$	9.00 -	13.75/lb
Ephedrine	$	-	1.25/oz
Epinephrine	$	-	.58/gram
Eucalyptol	$	-	4.00/lb
Eucalyptus oil	$	2.00 -	3.10/lb
Eugenol	$	3.90 -	4.00/lb
Fennel oil	$	-	10.00/lb
Fennel seed	$	.57 -	1.07/lb
Foenugreek seed	$	-	.37/lb
Garlic oil	$	-	35.00/lb
Geraniol	$	5.00 -	12.00/lb
Geranium oil	$	21.50 -	69.75/lb
Ginger	$	.46 -	.88/lb
Ginger oil	$	24.00 -	40.00/lb
Ginger oleoresin	$	-	22.00/lb
Grapefruit oil	$	1.15 -	2.00/lb
Guaiacol	$	-	2.60/lb
Guaiacwood oil	$	-	2.60/lb
Guar gum	$	.79 -	1.24/lb
Heliotropin	$	8.25 -	9.00/lb
Hemlock oil	$	-	8.00/lb
Henbane leaves	$	-	.55/lb
Inositol	$	-	24.00/kilo
Ipecac root	$	-	40.00/lb
Jojoba oil	$	90.00 -	100.00/gal
Juniper berry oil	$	55.00 -	65.00/lb
Karaya gum	$	1.75 -	2.00/lb
Kola nuts	$	.60 -	.65/lb
Laurel leaves	$	.52 -	.86/lb
Lavandin oil	$	5.25 -	7.50/lb
Lavender flowers	$	.65 -	.75/lb
Lavender flower oil	$	11.75 -	15.45/lb
Lemon oil, Argentina	$	6.50 -	7.00/lb
Lemongrass oil	$	-	8.15/kilo
Licorice root	$	.40 -	.95/lb

SOURCE: Chemical Marketing Reporter, 1982.

language on the computer facilities of the Washington Computer Center.)

First, locations for which date palm has been reported were retrieved and their climate parameters analyzed. The result is the range of climates which would be searched for; only 13 locations report date palm at present and the application of statistical methods is only suggestive of the palm's ecological tolerances and not definitive.

The arithmetic means of several climatic parameters for our small sample of stations suggest that ecological optima for date palm are approximately: average annual precipitation ca. 1,000 mm, average annual temperature ca. 23 °C. Seasonality of the infrared optimal climate is not apparent from arithmetic means, but the minimum values for monthly rainfall and temperature suggest a sustained warm summer (temperature 21 °C or higher for each month) and a coldest month with an average temperature not less than 8 °C. Precipitation peaks in the spring and autumn and a driest-month average precipitation of 4 mm suggests that a dry period is required, and appears to coincide with the temperature minima.

To select candidate climates from our climate file which contains data for more than 18,000 meteorological stations around the world, several assumptions were made based on the information above. This illustrates how AEGIS can be used to approximate the potential range of a given crop based on some knowledge of the crop and within the limits of reliability of the data from the file containing known distributions. First, stations were selected that had an average June temperature figure in excess of 20 °C, a January temperature figure not less than 8 °C, a July precipitation figure not less than 6 mm, and a continentality (Conrad's index) between −8 and 31 mm (the range found for those stations reporting date palm). This yielded 862 stations, many in Latin America. As some of these were found to be characterized by sustained rainfall throughout the year, additional constraints were added to improve the seasonality match: either the February or July precipitation was not to exceed 10 mm (for Southern and Northern Hemispheres, respectively), and the annual average precipitation was not to exceed 1,500 mm. (The minimum reported for date palm was 140 mm.) This generated a printout of 125 stations, including the following in Latin America:

Brazil: Araquai. Ecuador: Milagro, San Cristobal, Portoviejo. Guatemala: Amatitlan, Castaneda, Guatemala City. Honduras: Comayagua, Tegucigalpa. Mexico: Abasolo, Acaponeta, Ahome, Alcozauca, El Burro, Calaya, Carbo, Carrillo, Cerritos, Chiautla, Cintalapa, Colima, Comonfort, Concordia, Coquimatlan, Cuautla, Cuernavaca, Dolores Hidalgo, Ejutla, La Esperanza, Etla, Flor de Jimulco, Gongorron, Guayamas, Huajuapan, Ixmiquilpan, Jonacatepec, Lagos, Lerdo, Manual Doblado, Mezcala Isla, Miahuatlan, Monte Puerta, Moroleon, Motozintla, Nazas, Piaxtla, La Providencia, Puente de Ixtla, Rioverde, El Rodeo, San Blas, S. J. de Guadelupe, San Marcos, San Carlode de Yautepec, San Miguel Allende, Santiago Valle, Sierra Mojada, Tamazula Giordano, Taxco, Tehuacan, Tlacolula, Toliman, Topolo Bampo, Tuxtla Gutierrez, Union de Tula, Ures, Zimapan, Zinapecuaro, Ameca, Guadalajara, Leon, Oaxaca, Penjamo, Salvatierra, Zamora. Venezuela: Barquisimeto, Guigue, Valencia.

If more time were available for this quest, the selection process could be refined by entry of more data on the actual occurrence of date palms correlated with weather stations, and particularly on the yield of the palms at such places. At present AEGIS has no yield data at all on date palms, though published reports surely exist. Such data would help decide whether the palms would do well, rather than merely survive, at the stations indicated above. Other refinements, such as better attention to the reversal of seasonality in the southern hemisphere, could improve this kind of approximating retrieval and, in the present case, probably increase the listing for Brazil.

Appendix II: Rating American Localities Suitable for Date Palm

by James Alan Duke

Rather tardily, I am responding to a request to identify localities in Latin America best adapted to the date palm. I am passing on some of the data to demonstrate methodology (with a copy to OTA, which requested that I prepare a paper on applications and uniqueness of our data base here in EBL).

First the caveats! I have intentionally devoted less than 4 hours to this question. I have asked Dr. A.A. Atchley of this lab to devote a similar amount of time but to use his own devices. I hope that some of our conclusions will be the same! One should devote 4 months, not 4 hours, to a feasibility study such as this. What we will both send you are approaches at climatic analogues, very crude ones at that.

Once analogous climatic stations are uncovered, soils, availability of water for irrigation, peculiar atmospheric conditions (such as the fogs in the Chilean-Peruvian desert), and many other factors must be assessed as well.

Here is a thumbnail sketch of some of the date palm's peculiar ecological "whims":

> It is very tolerant of alkali soils and can grow in soils containing 3 to 4 percent white alkali, but to bear well, the palm's roots must be in a stratum with less than 1 percent of alkali silts.
>
> Grown ideally where the permanent water table is within 9 to 16′ of the soil surface. At least 8 to 9 acre feet of irrigation water per year is necessary for good production on bearing palms.
>
> Daytime temperatures of 50° C are tolerated. For proper ripening of fruit, the mean temperature between the period of flowering and ripening should be above 21.2° C rising to 26.7° C for at least a month.
>
> Finest date varieties require 3,300 units of heat, a unit being defined as a degree above a daily mean of 64.4° F between the flowering, fruit development, and ripening periods.

Israelis blame some of their problems on inability to control flowering time (it takes 6 months for fruits to ripen). There can be some control by withholding irrigation during fall and winter. There must be no rain during flowering time. An average temperature of 30° C is good for proper ripening. Winter temperatures below −8° C (ca 17° F) are harmful.

Any good soil that is not too heavy will do. In clean soil, a little hard water is acceptable; but a combination of alkaline soil and salty water is too much. Dates do well even where there is a crust of salt on the soil surface. If, in the top 2 to 2.5 m, there is a 30 cm layer or strata with 1 percent alkalinity, the date roots will "find" the strata and flare out there.

Indio, Calif., has long been a center for study of American plant introductions of the date palms. The Indio station is rumored to be in jeopardy, considered by some as excess government property, at least in part. Jim Carpenter (714-347-3414) should be consulted. He is one of America's leading experts on date palms. He could probably point out flaws in this 4-hour document. However, we are proud of our ability to identify rough climate analogues, once the specialists tell us what is required.

The following places are reported to produce good date palms:

	ECOSYSTEMATIC		*ECOSYSTEMATIC*
Place	*Code*	*Place*	*Code*
Aswan, Egypt	0026	Yuma, Ariz.	0122
Fayum, Egypt	0021	Beer Sheba, Israel	0219
Ciza, Egypt	0020	Bagdad, Iraq	0123
Thermal, Calif.	0123	Basra, Iraq	0224
Mecca, Calif.	0121	Alexandria, Egypt	0220
Indio, Calif.	0123	Tempe, Ariz.	0220

The first two digits of the ecosystematic code correspond to annual precipitation rounded off to the nearest decimeter. The second two digits correspond to annual mean temperature rounded off to the nearest° C. Monthly totals should also be consulted in a more refined feasibility study.

One can then look for comparable examples in a Table of Ecosystematic Values for Mexico and see that Baja, California, has several localities with identical ecosystematic codes to those for some of the better date producing localities—e.g., Comondu is analogous to Bagdad and Indio, Magdalena to Yuma, etc. Based on annual climatic averages alone, one might consider Comondu or any other place in Latin America with a ecosystematic code of 0123 to be a possible target for date palm cultivation. Several places in Peru (e.g., El Alto, Bededero, Campo de Marte, Cayalti, Talera, Trujillo, Zorritos, etc.) have ecosystematic codes similar to some of those listed above and could be investigated as date palm targets.

This is just a superficial sketch. While I would bet on the Baja, California, stations, I would be leary of fog in Peru (unless hand pollination were guaranteed) and in all cases I would question the availability of irrigation water equivalent to 2,300 mm/year.

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ECOLOGICAL PERSPECTIVES ON THE INCREASING USE OF PLANTS TO PROVIDE USEFUL PRODUCTS

(A Review of the OTA Workshop Papers)

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Introduction

Breadth of ecological implication

The suggested broadened use of the world's plant resource base has ecological implications which are considerably more far-reaching than those implied by most alternative technology choices. These potential ecological impacts should be considered as underscoring the significance of this OTA study.

In the eyes of at least one analyst (14), the mechanical-industrial age of the late 1800's and early 1900's gave way during the 1940's to the age of alchemy. We have learned to synthesize innumerable useful products from raw materials. In some instances those raw materials are readily available and seemingly inexhaustible. However, a large proportion of our technological efforts are directed toward developing products from raw materials that are in finite supply—in particular, fossil hydrocarbons. The age of alchemy seems to have been characterized by a narrowing of our technological vision.

In recent years, unlocking genetic codes and developing techniques for cellular manipulation of genetic materials have renewed the interest in developing biological processes and materials to create products useful to humankind. These new techniques may provide the transition tools to take us from the age of alchemy to that of algeny, in which there would be a greater reliance on biological rather than nonliving, chemical processes. It seems that the energy and resource consumption of the chemistry-based technologies of today are nonsustainable. In addition, the environmental loading of slowly biogradable or nonbiodegradable materials has adverse implications for the quality of human life and for native flora and fauna.

Many people are not aware that the new biotechnologies are as dependent upon the availability of existing genetic material as they are on raw materials. For the foreseeable future, we will depend primarily upon existing life forms rather than on artificially synthesized life constructed according to design from some sort of "basic building blocks." The new technologies enable the rather rapid shaping and molding of existing genetic material into more productive and useful forms. The identification of those potentially useful biological materials is the focus of work surveyed in this study.

Far-reaching issues of direction and paradigm

The present dependence on a limited number of plant species as sources of most of our raw products and food permits use of only a small fraction of the Earth's surface for production of useful products. The demand for those products often outstrips the productive capacity of the "arable" land used to produce them. As our technologies focus on an ever-narrowing list of commercial crops for food, fuel, fiber, and industrial products, and as growing demand forces greater production of these few commodities, there is increasing evidence of adverse environmental impact and a subsequent decrease in our production resource base. Nonsustainable levels of soil erosion or ground water depletion are evidence not only of deficient production technologies but also of growing crops that are too resource-demanding. Forcing corn, wheat, soybeans, or other annuals onto land that will not sustain them is a short-term solution to product supply.

The vast areas of land now considered to have low production potential for the present intensively cultivated crops may be considerably more productive with carefully selected and properly managed alternative crops. Many lands which are now commercially unproductive could be cropped safely to a wide range of perennial crops identified as sources of useful products. Jojoba and sisal for semiarid environments are excellent examples. There are also many potentially valuable biocidal compounds produced in species adapted to semiarid environments. These marginally productive environments (as measured by their ability to produce our current major annual crops) typically are areas of environmental degradation and human poverty. Broadening our crop focus and making use of potential production resources could help arrest resource deterioration and improve the quality of life in these areas.

Benefits of using biologically produced materials

One of the adverse effects of "the age of alchemy" has been the environmental loading of synthetic materials, particularly biocides. While biologically produced materials may have equally disruptive short-term effects, they are biodegradable and rarely persist over long periods, so cause little, if any, long-term disruption. Once having identified such compounds, it is often possible to synthesize them. In the case of the insecticide pyrethrum, however, insects have not built up a resistance to the naturally occurring form, but they have to the synthetic form (2,4).

A disadvantage of relying on plant-derived biocides is that they seldom have narrow selectivity and do not move systematically in plant tissue. They can be used near the time of harvest, however, because of their short residual time.

The importance of genetic diversity

Much has been written in recent years on the subject of crop diversity. The widespread incidence in the United States in 1970 of corn leaf blight, which caused an estimated 15 percent loss of our corn crop, aroused considerable interest and concern. The National Academy of Sciences' study "Genetic Vulnerability of Major Crops" (5) became the benchmark to a series of subsequent reports. The report's primary recommendations focused on increased emphasis on plant breeding and improved germ plasm collections. Subsequent NAS reports have dealt with the desirability of increasing the world's crop base (6,7,8,9,10,11,12). There continues to be considerable alarm over decreasing crop genetic diversity (15). Increased crop diversity reduces the buildup and spread of plant pathogens and insect pests. From the standpoint of the individual farm, a variety of crop options vastly increases the economic stability of the operation and provides the "tools" needed to structure a resource-efficient operation. The vast array of crops grown on a typical Chinese vegetable farm nicely illustrates the point (3). Having an array of crop options permits the establishment of rotations to reduce cost of controlling weeds and soil-borne insects and diseases.

The energy saving of greater self-reliance

The identification of plant sources for industrial products, pharmaceuticals, and pesticides would have a positive impact on developing countries. In some cases the new crops could provide the basis for a new export industry, but the greatest impact would be to permit a greater degree of self-reliance. Having a greater capacity for in-country production of raw materials rather than a worldwide network of product flow with highly centralized synthesis and distribution reduces the service, handling, shipping, and, ultimately, the energy costs of a product. In the future energy-and-resource-limited world, a new balance between production and service costs must be reached. We will no longer be able to afford the energy-intensive open supply loops of the past (1).

The USDA Economic Botany Laboratory's Data Base on Minor Economic Plant Species

by James Duke

Much, if not most, of our crop movement and related agricultural development work over the past several decades has, ironically in an age of computer and systems science, been done empirically (3). The USDA's data base on minor economic plants, if extensively used, would help match crops to their "best fit" environment. It would assist significantly in development planning by suggesting the best crop options for target environments and by helping to minimize crop development efforts in environments that are marginal or unsuited to the crop species. Marginal environments typically mandate the use of extreme measures, either in modifying the environment or in protecting the crop. Under stress conditions, most crops are more sensitive to a pest or pathogen. A "best fit" crop-environment situation generally leads to optimal crop-environment biological stability with minimal need for drastic intervention with biocides or other harmful production inputs or technologies. The ecosystematic file described by Duke has potential for the greatest positive environmental impact of all technologies discussed in this workshop.

The USDA data base can play an important role in dealing with the spread of pests or diseases. Plant scientists recognize the need for extreme caution when moving plant materials. There are elaborate protection mechanisms to safeguard against the spread of pests and diseases. The recent movement of the Mediterranean fruit fly to California is an example of a detrimental introduction. In all likelihood this pest was introduced through transporting produce rather than plant genetic material. One finds, however, that when dealing with "exotic" or noncommercial plant species, the normal plant quarantine coverage often is less stringent than with commercial species. If a little-known species does not appear on the list of "regulated" species in a country, it often can be moved in or out freely. Most scientists, in their concern for making rapid progress, hope for ease of moving materials, despite the dangers. It seems that the present U.S.

quarantine laws with respect to movement of seed and plant materials are adequate, but budgets, staff, and facilities are not adequate to accomplish much more than perfunctory formalities.

There is one further consideration concerning the biological stability of materials moved to different environments. The USDA's ecosystematic file is based on environmental classification according to various factors of the physical environment. The species composition of the plant flora constitutes a second order of classification. As Dr. Duke suggests, this helps define environments where a given species can be expected to perform well. However, more attention should be paid to the pest/pathogen balance of a species. If a species has inhabited a given environment for decades or centuries, it and its pests and pathogens can be expected to have coevolved so they are in relative equilibrium. That is not the case with a species introduced into an environment that is physically similar. Even if the introduced seed or plant material has left behind its complement of pests and pathogens, in all likelihood some of the insects or pathogenic organisms in the new environment will be able to use it as a new host. There is little, if any, way to predict or guard against such occurrences with information available today. Such unknowns should not impede crop movement, but the crop should be carefully monitored in its new environment. The USDA Economic Botany Lab's pest file could be helpful in providing information relevant to crop introductions, especially if the file is expanded to record the ecological amplitudes of pests and diseases.

In light of the potential of the USDA data base for providing long- term environmental benefits, the lack of sufficient funds and the inactivation of such a useful and beneficial program are regrettable.

Information Gathering and Data Bases That Are Pertinent to the Development of Plant-Derived Drugs

by Norman Farnsworth and William Loub

Most of the comments on the Duke paper apply equally to this work. The desirability of diversifying our agricultural crop base supports any efforts leading to that end. Despite the wide ranging potential benefits of developing plant species for pharmaceutical extracts, U.S. pharmaceutical companies show little interest in this field.

Farnsworth and Loub state that "typical industrial drug development has increasingly involved synthesis of molecules based on structure-activity relationships" and that "not a single pharmaceutical manufacturer in the United States is involved in a research program to discover new drugs from higher plants." This pattern is also followed by companies developing agricultural biocides.

The major ecological problems in researching and developing pharmaceuticals from plants involve the movement of plant materials and depletion of natural sources of diversity. In the screening phase, it is usually desirable to collect plant materials directly from their native habitat for laboratory processing, extraction, and testing to save money and time. Where materials are to be used for laboratory processing, precautions must be taken to minimize the danger of spreading unwanted organisms. This requires constraint on the part of the research laboratory to avoid replanting materials not screened for propagation. Once a species is identified as having potential, however, greater quantities of material are needed for more extensive extraction and testing. The extent and amounts of the species should be evaluated before extensive and voluminous collecting is done so as not to deplete existing genetic diversity. This could severely limit future breeding work. Likewise, once a useful product is known and commercial extraction begins, agricultural production of the species must be started if the species is not plentiful in the wild. A high price for a raw product of a wild species can quickly drive the species to extinction. This is true for the entire range of useful plant products, particularly those of high value.

An Alternate Use for Tobacco Agriculture: Proteins for Food Plus a Safer Smoking Material

by Samuel Wildman

An overriding issue in the development of tobacco is the desirability of subsidizing research and development of a crop that has a large economic demand but few socially redeeming features to balance its high social costs.

The crop has severe adverse environmental impacts. When grown in the traditional manner, it quickly reduces the natural soil fertility. The many field operations, including cultivations and vehicular and field worker traffic, lead to compaction and deterioration of soil structure. The soils of the warm, humid tobacco areas are subject to erosion.

These problems could be alleviated by growing tobacco in a carefully planned matrix of cover crops, rotations, and limited tillage systems, so they are not necessarily overwhelming. Of even greater concern are the large quantities of chemical inputs needed for field production.

It is argued that biomass production reduces the need for insecticides. The 10 to 12 sprayings required for a crop of smoking tobacco can be reduced considerably if processing for protein extraction can avoid the "cosmetic" quality restrictions of whole-leaf tobacco. The problems of seedling establishment require either "clean" or previously unused land or fumigation. Fumigation is an extremely environmentally disruptive process. Depending on the materials used, the presence of the chemical fumigant can be of short duration, but the disruption of soil microflora and microfauna is longer lasting. The alternative of transplanting requires less area in seedbed but higher costs of growing and handling the transplants.

From any standpoint, tobacco is an energy-intensive, fertilizer- intensive crop with high environmental impact. A saving factor under present practice is that commonly it is grown in relatively small fields because of the allotment system and labor requirements. This mitigates its adverse effects to some extent. It is conceivable that the more concentrated area production necessitated by a processing facility would present greater environmental problems.

An energy analysis of tobacco production and of its leaf protein extraction should be accomplished before much more work is done. In the long term, energy costs closely parallel dollar costs. There must be crops that could produce equal quality leaf protein at considerably lower cost. From an environmental standpoint, it seems that the greatest contribution of a tobacco leaf protein industry would be to decrease tobacco acreage.

The statements in Wildman's text that "agriculture in developing countries in the tropics is notable for lack of crops of high protein content" or that "soybeans also cannot be grown in the tropics" simply are not true. Tobacco, in fact, has increased pest problems in tropical environments so that it is even harder to grow it.

Leaf Protein Extraction From Tropical Plants

by Lehel Telek

The work of screening tropical plant materials for protein content, fractionation properties, and evaluation of the resultant protein fraction is environment-neutral. Telek's paper points out nicely, however, the complexity of production systems required for effective use of protein extraction technology. With production of standard human food or animal feed-grade protein, the integration of several industries is essential. The complexity of interactions between those industries and the environment render a simplistic summary of environmental impact of little use. The following types of analyses of each industry segment may be required for any particular environmental zone of production:

1. Raw product production impact—energy cost, environmental impact of the crop production (soil loss, ground water use and impact, biocide requirements and impact);
2. Raw product quality—the production-related materials that may be present to contaminate the protein and product;
3. Extraction process impact—energy requirement; cost of holding air- and water-effluent discharges to acceptable volume and quality; cost of solvent recycling or disposal;
4. Impact of related industries that use various plant fractions.

At this early stage in the development of plant protein isolation processes, an analysis of energy efficiencies of alternative protein use pathways would be in order. Comparing whole-plant use by various fish and animals with fungal or bacterial digestion would give rough estimates of threshold energy efficiencies that must be achieved by fractionation systems in order to be competitive. As far as possible in these analyses, it is essential to internalize the costs for avoiding environmental disruption. Conservative estimates by today's standards of permissible environmental loading would be appropriate if the model is to be applicable in the future. Such analyses will be complex and costly and should not be required for each enterprise being considered. Such analyses would be useful at this early developmental stage to provide guidelines and estimates of the practicality of a given pathway. Few data are available, and energy and cost effectiveness of the fractionation methods are difficult to assess.

Third World production of many, if not most, of the species tested—particularly the perennial crops—presents no environmental problems not already well recognized for those species. Given a choice, one would prefer to grow the crop requiring the lowest nonsolar energy input and having the greatest amount of stability with respect to pest and disease incidence.

Insecticides, Insect Repellants, and Attractants From Arid/Semiarid Land Plants

by Martin Jacobson

With increasing emphasis on integrated pest management, there is increasing opportunity to use a wide range of materials affecting insect behavior. Because many of these materials seem to have evolved to a greater extent in arid/semiarid plants, a search for such compounds could be productively targeted at these plants. It is unfortunate in that production in such environments on a commercial scale must be carefully managed with respect to ground water use and soil conservation. As with all other plant-derived products, the recycling or disposal of solvents used in the process is important.

The areas of plant-derived biocides and insect behavior modifying compounds has potential for having a significant impact on the ecological effects of modern agriculture. Many of our present synthetic biocides are extremely persistent in the environment, and their accumulation is the source of considerable concern.

An example is Temick, an insecticide that has been used by many Long Island potato growers against the Colorado potato beetle. Because of its persistence it has leached through the sandy soils of Long Island to reach ground water aquifers in relatively high concentrations. In years past a material comprised of ryania, rotenone, and pyrethrum—all plant-derived insecticides—had been used with equal effectiveness. Its use was discontinued because of the lower cost of Temick and other synthetic materials. An effort is under way to bring back the plant materials to replace Temick.

With the exception of pyrethrum, a commonly used household insecticide, the work on commercial use of plant insecticidal materials has been limited to small companies specializing in "alternative" agricultural products. Little indication exists of industry interest in such products, a situation analagous to that of the pharmaceutical industry.

A wide range of insect-behavior-modifying substances that have little biocidal activity exists in plants. Work at Rodale Research Center shows that camphor, a compound present in many aromatic plants, has strong insect-repellant activity. Camphor wood, in fact, has been used from ancient times because of its durability. Little work has been done to identify such compounds. These compounds, along with plant-derived insecticides, could have a positive and widespread impact on agricultural systems by replacing many of the more environmentally disruptive materials now commonly used in agricultural production.

Environmental impact studies should be conducted for plant-derived pesticides. Most botanicals are nonselective but of relatively short persistence.

Molluscicidal and Other Economic Potentials of Endod

by Aklilu Lemma

Endod has broad-spectrum biocidal activity as a molluscicide, spermatocide, insecticide, and bacteriocide. Here, again, the range of its effects should be studied before it is used widely in the United States. Its effects on humans, wildlife, fish, and a broad spectrum of biological organisms likely to be affected by common application should be determined. The research detail and resultant cost for this work seem to necessitate the creation of patent rights and protection which would make the expenditure attractive to industry. Government support in the form of research funding may also be essential.

Each of these potential crops should be included in a refined USDA data base on minor economic plants species, and their likely growing areas should be determined before a major research commitment is made. If a species has fairly broad production area potential, it would be a more attractive investment.

The Role of the Alkaloids of *Catharanthus Roseus* . . . .

by Gordon Svoboda

Many of the points raised previously apply to this paper. They are the:

1. need for careful collection of the crop in the wild prior to production;
2. need for caution in moving plant materials;
3. need for analysis of recycling or disposal of production solvents and chemicals; and
4. potential for residues of production chemicals to find their way through the extraction process.

The energy cost of such extraction is less relevant because the product is of low volume and high value.

The production impact should be monitored; however, with extremely small acreage the production is relatively easy to frame within production of rotation crops and other environment-protecting practices. A significant adverse environmental impact from crop production is unlikely.

Chemicals From Arid/Semiarid Land Plants: Whole Plant Use of Milkweeds

by Robert Adams

Most of the previous comments relevant to dryland agricultural production apply here. The dry areas where milkweeds have been tested commercially are very prone to erosion. In evaluating the production costs, it will be necessary to factor in conservative erosion control practices from the start. Zero till, crop overseeding, sod culture, narrow strip cropping, and a range of other options should be evaluated. In the near future solutions to erosion problems must be found. Those solutions will have associated costs which will have to be included in the crop production cost.

The potential of milkweed or similar crops as weed pests should be evaluated. Nevertheless, milkweed, with its potential as a dryland crop in a low rainfall area, might be able to replace irrigated crops in areas now experiencing ground water depletion.

Marine Plants: A Unique and Unexplored Resource

by William Fenical

This area of study is quite different from those of terrestrial plants. Areas of environmental concern include:

1. The undesirability of studying "fragile" marine organisms for potential use. For instance, species of coral that are limited in extent and slow-growing probably could not be used effectively even if they contained useful compounds. The studies should be limited to those that are either relatively plentiful or not too difficult to culture.
2. The presence of contaminants in the marine environment can be a limiting factor for some species or products if they are difficult to remove in the fractionation process.

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POTENTIALS FOR EXTRACTING PROTEIN, MEDICINES, AND OTHER USEFUL CHEMICALS FROM PLANTS: SOME SOCIOLOGICAL OBSERVATIONS

(A Review of the OTA Workshop Papers)

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Introduction

The extraction of useful chemicals from plants has a number of potential benefits from a sociological perspective. The major societal benefits would include substitution of domestically produced commodities for petroleum and other imports, thereby alleviating balance of payments problems; more productive use of resources, particularly in marginal farming areas; and diversification of the U.S. agricultural system, which would permit market expansion without farmer dependence on increasingly expensive and politically problematic Federal subsidies from traditional commodity programs. Some degree of government subsidy and other forms of intervention probably will be required to stimulate farm- and industrial-level plant extracts industries. Such government intervention may be greatly preferable to export subsidies for foodgrains, feedgrains, and other agricultural commodities in light of problems of aggravated balance of payments deficits and the farm recession.

This paper addresses sociological aspects of plant extraction in the United States and its agricultural industry. The paper is organized into six sections. The first provides some general comments on the socioeconomic context of efforts to develop plant extract industries. The second discusses constraints on plant extract development relating to the land resource base. The third is devoted to research and development (R&D) activities necessary to undergird commercial scale plant extract industries. The fourth and fifth examine possible impacts of plant extract development in terms of the organization of agricultural production and the organization of nonfarm industry, respectively. The final section explores various policy and political issues that have or may emerge in stimulating an expanded plant extract industry in the United States.

The Current Socioeconomic Environment for Developing Plant Extract Industries

All 10 papers presented at the OTA workshop support the expansion of plant extract industries. However, it is essential to recognize that the present economic era is not entirely propitious for the types of initiatives proposed in the papers. Thus, a realistic view of potentials for extracting proteins, pharmaceuticals, biocides, and other useful chemicals from plants must be tempered by a variety of conditions that constrain industrial development in general and that of plant extracts in particular.

The dominant feature of the contemporary United States and world economy is global recession. That the recession has been and continues to be global reminds us that all manner of magical cures for national economic ills must be taken with a grain of salt and that we must view the situation more broadly as a fundamental point of global economic reorganization. It is crucial for policymakers to recognize that the conditions of the post-World War II economic boom are unlikely to be replicated and that policies for the 1980's must reflect new socioeconomic realities. This is both promising and discouraging for plant extracts. Much of the thrust behind stimulating the plant extracts industries is "import substitution." The character of trade relations in the new economic order that will emerge during the late 1980's* will make it attractive to substitute domestically produced substances for chemicals and raw materials that we have imported during the past several decades. At the same time, however, the very conditions that characterize a recession—capital scarcity, fiscal crisis, economic uncertainty, rigidities in public policy—make it more difficult to expand new industries rapidly.

Capital scarcity will certainly be a key constraint to widespread development of plant extract industries. "Real" interest rates (the nominal interest rate less the rate of inflation) remain at levels unprecedented during the post-World War II period, despite recent declines in the prime rate. High interest rates make it much more difficult for new industries to attract capital and greatly increase the riskiness of new ventures with uncertain markets and production technologies.

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*These trends will likely involve: 1) further decline of traditional U.S. manufacturing industries (e.g., autos, steel) and increased competition with the firms of foreign countries (especially Japan, South Korea, Taiwan, Singapore, and Hong Kong), and 2) an eventual tightening of markets in petroleum and other raw materials. These two trends suggest continuing balance of payments problems, making import substitution industries such as plant extracts quite attractive.

In addition to capital scarcity, economic recession involves several other conditions adverse to expansion of new plant extract industries. First, the recession's downward pressure on inflation rates, especially when combined with restrictive monetary policy in the United States, tends to make imports cheaper relative to domestically produced commodities. Thus, to the degree that plant extract industries involve import substitution, they will be attempting to produce commodities domestically that have been imported at a time in which a strong U.S. dollar lowers the relative price of these imports. This has been the case particularly for fossil fuels and other raw materials, against many of which domestically produced plant extracts would compete. Raw material prices are heavily influenced by the level of demand, which in turn is heavily influenced by general economic conditions. For example, declining energy demand has led to dramatic declines in the real price of energy, which now is only slightly higher than before the Arab Oil Embargo of 1973-74. Global economic recovery, which is likely to proceed slowly over perhaps a 5-year period, will lead to a tightening of oil and other raw materials markets and will than cause rapid increases in relative prices of these raw materials some years later. However, the fact remains that plant extracts that compete against imported raw materials or industrial feedstocks must temporarily buck an otherwise strong logic of increased import dependence on raw materials. Wise policymakers will recognize, however, that raw materials markets will tighten over the next decade and that the most desirable time for front-end R&D and other subsidies for the development of plant extract industries is now. For most plant extract commodities, a decade will be required to conduct further research and establish a stable position in domestic markets. Thus, advance planning will be necessary to bring import substituting industries up to scale before U.S. industry falls victim to the next round of hyperinflation of raw materials prices.

Another feature of global recession is the political-economic volatility of trade. Recession on a global scale tends to increase nationalist sentiment, especially in regimes that blame their economic problems on "unfair" foreign competition (see, for example, *Business Week* (4)). Economic nationalism tends to involve protectionism vis-a-vis imports and export subsidies to increase international sales of domestic commodities. Economic nationalism thus makes trade-related investments especially risky; import substitution investments can be undermined by other countries' export subsidies, and where investments such as those in plant extracts industries are premised on exports, export sales can be undermined by protectionist policies.

Another feature of the current socioeconomic conjuncture is the increasing export dependency of the United States with regard to its basic foodgrains, feedgrains, and oilseeds. Roughly 35 to 40 percent of the value of U.S. agricultural production is exported, making farmers' incomes highly dependent upon maintenance or expansion of export markets. Moreover, virtually all forecasts of agricultural markets over the next several decades indicate that a growing proportion of farmers' gross receipts will be from exports (8,12,17). However, the current global recession, combined with the 5-year legacy of the executive branch suspending certain international grain sales as a foreign policy lever, has undermined agricultural export earnings and exacerbated the farm crisis (16). Thus, counterbalancing an otherwise gloomy situation for plant extracts industries deriving from international economic stagnation, the disproportionate burden of economic stagnation borne by farmers will no doubt make agricultural diversification look increasingly attractive for both producers and Federal officials. Diversification of markets can benefit producers in obvious ways, while the Federal Government should welcome strategies that can shrink costly Federal commodity programs.

Most plant extract commodities discussed in the 10 workshop papers will require considerable additional R&D investment for commercial scale-up. However, current conditions for expansion of R&D in the public sector are unfavorable. Over the past several years there has been stagnant or declining support by the Federal Government for nonmilitary R&D, including agricultural research.* Moreover, Federal fiscal austerity and accompanying cutbacks in Federal support of applied research have a questionable justification—that the private sector should shoulder a greater burden for applied research, while publicly funded research should be confined largely to basic research. To be sure, science policy should not encourage duplication of effort by underwriting public research that focuses on problems more efficiently explored by the private-sector. But such duplication of effort is not frequent or unwarranted, and the withdrawal of public support from applied research relating to industries, such as plant extracts, could be quite crippling. For example, front-end research required to stimulate plant extracts industries is extremely varied and requires discrete sets of trained researchers and suitable research facilities. A large share of these research tasks could be accomplished efficiently through grants to established research teams in universities or private research organizations. Wise science policy must recognize that the now-popular image of creating division of labor between university-based "basic" and private-sector-based "applied" research is suitable primarily for "high-tech" sectors within large multinational firms with well-funded, established research organizations. It would be unrealistic to expect small- to medium-sized businesses to shoulder the burden of R&D in numerous diverse areas ranging from agronomy, plant breeding, physiology, microbiology, plant pathology, entomology, engineering, bioassay, synthetic organic chemistry, market research, etc. The current climate of retrenchment in public support of applied research thus will be a substantial barrier to the development of the plant extracts industries. Congress should be urged to consider more carefully the general long-term implications of short-term savings in R&D spending and the specific problems such policies will cause for the expansion of the plant extracts sector.

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*The Reagan administration recently appears to have reversed itself with regard to the priority placed on basic science research funding. The National Science Foundation apparently will receive a substantial funding increase in real terms (5). However, it would appear that Federal funding for applied research will experience stagnation in real terms over the next several years.

A final aspect of the current socioeconomic milieu that will have crucial implications for industries seeking to extract useful chemicals from plants is the emergence of genetic and cellular manipulative technologies such as protoplast fusion, cloning, tissue culture, recombinant DNA, and immobilized enzymes. While these technologies will have positive long-term implications for substituting natural substances for petrochemicals and other nonrenewable resources (18), these technologies may at some prior point discourage investment and innovation because of the threat of rendering conventional plant extracts technologies obsolete. For example, recombinant DNA and industrial microbiology techniques may displace field production of plants and chemical methods for extracting fractions of plant tissue. To help avoid this conflict, it might be prudent for the Congress to encourage biotechnology research firms to take the lead in selected areas of plant extracts technologies. There are several biotechnology research firms (e.g., the International Plant Research Institute, Cetus, and Agrigenetics) that are oriented heavily to research on agricultural crops and other higher plants. Their agricultural capability and growing expertise in industrial microbiological aspects of industrial scale-up may make these firms highly suited to the development of plant extracts technologies requiring agronomic and plant breeding research. At the same time, it should be recognized that venture capital biotechnology firms will have proprietary interests. Where it is undesirable for research results to be proprietary property, R&D subsidies should be directed to public research institutions such as State agricultural experiment stations or USDA's Agricultural Research Service.

The Land Resource Base

Most potential plant extracts discussed in the 10 workshop reports involve cultivation and harvesting of higher plant species. In some cases (e.g., endod, neem), the species are perennials native to the production region, and expanded use of these plants would require little or no increased spatial or ecological "demand" on the land resource base. However, several plants—especially guayule, crambe, jojoba, lesquerella, vernonia, kenaf, tobacco, milkweed, and conventional oilseed crops—if used for plant extracts industries, would have substantial implications for the quantity and quality of U.S. land resources. This section thus will provide some observations on the degree to which the U.S. land resource base would be adequate to support the cultivation of 60 or more million additional acres of crops devoted to plant extracts.

The adequacy of the U.S. land resource base is a very complex issue and has received increased attention over the past decade (1,7,11,13,20). Land resources will be more than sufficient to feed the U.S. population and provide industrial raw materials (e.g., cotton, sugar, wool, wood) for the short term. However, the adequacy of the land resource base over the long term depends on certain unpredictable phenomena about which surprisingly little is known.

Probably the most unpredictable aspect of demand for land is the future level of export sales. Over the past decade, roughly 35 to 40 percent of U.S. agricultural production has been exported and, as noted above, the consensus among econometric predictions of future trends is that it will increase perhaps to the point where over half of U.S. agricultural production will be exported by 2010. However, these predictions have been based on relatively favorable assumptions about global economic growth, and if the next few decades are characterized by continued economic stagnation, the level of export sales and hence demand on land resources may be considerably less than most analysts have anticipated. Further, levels of export sales are not derived entirely from "natural" economic forces. Certainly, much of the rapid increase in farm exports over the past 15 years has been accounted for by political considerations. Exports have long been sought as a means to dispose of farm surpluses and to increase farm income without Federal subsidies. The 1970's and 1980's reflect a continuation of this expectation which rarely has been fully realized. In addition, farm exports have acquired added political importance due to their role in reducing balance of payments deficits. The fact that the next several decades promise little alteration in political conditions favoring the stimulation of export sales suggests prudent caution: export sales may not increase as rapidly and steadily as was predicted a few years ago, but the most likely prospect is to devote increasing numbers of acres of farmland to producing feedgrains, foodgrains, and oilseeds for export.

A second unpredictable factor is the nature and pace of technological change in the direction of increased land productivity. It has been generally acknowledged that the 1970's was a decade of relatively stagnant land productivity, and many observers felt that agricultural researchers had encountered limits to productivity growth through conventional plant and animal breeding (15). However, at the same time that dire predictions were being made about meager land productivity increases in the U.S., biotechnological techniques (e.g., genetic engineering for increased photosynthetic efficiency) were emerging that promised continued advances in per acre yields. Unfortunately, these new technologies remain at such an early stage of development that it is difficult to speculate on the timing or consequences of their commercial deployment, and hence on their impacts on the land resource base.

Complicating international trade and technological uncertainties about demand for land resources are disagreements over recent historical trends that have affected the quantity and quality of land resources available for production of agricultural and industrial raw materials. The first is the extent and significance of the loss of agricultural land to urban development, water impoundments, highways, airports, etc. While it has been assumed that irreversible conversion of farm land to other uses has been significant (approximately 3 to 5 million acres per year), recent evidence questions the accuracy of these data and argues that this loss of agricultural land will be relatively trivial in the next several decades (20). The second area of disagreement has focused around soil erosion and related forms of land degradation. While it is generally recognized that soil erosion in many areas of the country remains unacceptably high, there is considerable disagreement over the degree to which land degradation will limit agricultural productivity in the future (7,8,17,19,23,24,26).*

One final complicating factor in anticipating the availability of land for plant extracts production is the extent to which land will be used to produce biomass energy. Late-1970's enthusiasm about using agricultural biomass for energy has, of course, subsided now that the real price of energy has been reduced to levels approaching pre-Arab oil embargo figures. Yet, petroleum markets may tighten again and resultant increases in the real price of energy may cause a significant allocation of agricultural land to energy production.

Of the 10 reports, that by Tankersley and Wheaton pays the greatest attention to land resource questions, primarily because the plant extracts potentials discussed in this paper have the greatest implications for pressing against the limits of the U.S. land resource base. Tankersley and Wheaton point out that "production of one-third to one-half of the industrial materials (presently) purchased abroad would demand about 60 million acres of cropland." While this increased demand on the land resource base would entail roughly a 20 percent expansion of land in crop production over the 1979 figure of 348 million acres, the authors are relatively unconcerned about plant extracts industries creating undue pressure on land resources. Two rationales undergird this argument. First, Tankersley and Wheaton cite data that there are "36 million acres of pasture and other land in farms that can be easily converted to the production of crops with little costs" and that the U.S. "has about 96 million acres of land that can be converted to crop production with more difficulty and cost than the 36 million acres cited above." Given that "the Nation's total cropland base . . . is 540 million acres" and "projections made by the Department of Agriculture . . . [that] about 462 million acres of cropland will be needed in the year 2030 to meet domestic and foreign trade demands for food and fiber," 78 million acres of cropland would remain to devote to plant extracts industries and other land uses. Be-

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*See also *Impacts of Technology on U.S. Cropland and Rangeland Productivity* (Washington, D.C.: U.S. Congress, Office of Technology Assessment, OTA-F-166, August 1982).

cause these 78 million "slack" areas are in excess of the 60 million acre estimate of the land required to substitute for one-third to one-half of industrial materials purchased abroad, the authors see little problem with regard to the adequacy of the land resource base. Second, the authors see clear public benefits associated with pressing up to the limits of the agricultural land base; "at that rate of utilization, there should be no need for farm commodity support or subsidization programs for food and fiber."

Several points can be raised about the inferences the authors have drawn from these data. First, I would urge a more cautious point of view with regard to the ease of conversion of land now used for pasture and other purposes into cropland. Most of this land is withheld from cropping for the simple reason that it is too steeply sloped, too poorly drained, etc. to justify cultivation in an intensive cropping regime. The authors quite correctly imply that noncropland "in farms" is easier to convert to cropping than land with no connection to operating farms. Nevertheless, there is by no means a consensus among researchers about the ease or cost of converting such land to crops.*

Second, Tankersley and Wheaton's arguments about the "96 million acres of land . . . " neglect a crucial problem in reallocating this land to cropping. Because much of this land is owned by nonfarmers and is being "used" (e.g., as recreational property), efforts to add this land to the effective cropland base of the United States will encounter two key problems. One will be transfer of control or ownership, since it is likely that this land will need to be leased or sold to farmers to be converted to cropping. Second, given that the land is not idle in the strict sense—i.e., the land is being enjoyed or otherwise used for some purpose that contributes to human satisfaction—returns from cropping the land must be fairly substantial to induce a shift from its current pattern of use.

Third, I have reservations about Tankersley and Wheaton's ideas on "utilization rate." The authors operationalize this rate as the number of acres of land in crops divided by the number of acres in the potential cropland base (times 100). The implication is that the higher the utilization rate, the more efficiently cropland resources are being used. A utilization rate approaching 100 percent should not be regarded as unambiguously desirable. As noted earlier, the extent of demands on the U.S. cropland base are difficult to predict three or four decades into the future. Therefore, a moderate "utilization rate" would seem to be more prudent than a rate approaching 100 percent. Intensive cultivation of marginal lands, even under the best circumstances, threatens to degrade the quality of this land and other resources (e.g., soil erosion and fertilizer runoff leading to sedimentation and eutrophication of lakes and streams). Moreover, a moderate utilization rate enables the society to have a land reserve which can be drawn upon in the event of unforeseeable circumstances. I suggest that policymakers be cautious in pressing the use of fragile lands to their limits and thus reducing land use options in the future.

In a certain sense, posing the issue as we have—asking whether the sum total of demands for agricultural land will exceed the supply of land—is unrealistic. The use of land will be determined in great part by market forces. Given this reality, it will be important, however, for policymakers to ask: which uses of land are essential or socially desirable and should be encouraged, and which are less essential and do not deserve public subsidies? My own view is that the use of land for both plant extracts feedstocks and low-intensity reserves of low- to moderate-productivity land serve the societal good, albeit in very different ways. Most importantly, as demands on the U.S. land resource base increase over the next decades, policymakers, essentially for the first time in history, will have to grapple with the costs and benefits of particular land uses and make explicit decisions to encourage or discourage particular uses of land.

Research and Development Aspects of the Plant Extracts Industries

The potential commercial crops discussed in the workshop vary greatly according to "front-end" R&D requirements. Even the plant sectors requiring only modest amounts of R&D before widespread commercialization becomes possible need a suitable R&D system that can produce continued refinements in on-farm production and nonfarm industrial techniques. Thus, much of the future of the plant extracts sectors will depend upon establishment of appropriate R&D systems that can facilitate breakthroughs and continued fine-tuning.

It is important to emphasize the particularly complex nature of plant extract research and development requirements. Most plant extract commodi-

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*Tankersley and Wheaton's optimistic assessments of the amount of land that can be converted into plant extracts production (and of the speed of this conversion) can be contrasted with the much more pessimistic results reported by Doering (9,10) with regard to converting noncropland for biomass energy production.

ties require a long chain of research tasks. This is, of course, most true for pharmaceutical commodities and somewhat less so for biocidal materials, given the necessarily long and careful procedures required for licensing of substances that might have deleterious impacts on humans or other life forms. Also, most of the plant extract commodities that involve agricultural production face R&D requirements spanning a variety of scientific disciplines. Perhaps the most difficult problem is that these agriculturally related commodities require agronomic and related research—the bulk of expertise for which lies in public, land-grant institutions—and industrial biochemistry and engineering research—the bulk of which is now privately funded and entered into on a proprietary basis. Moreover, the situation becomes even more complex if by-product use is required to begin commercial scale-up. Coordination and control will be potentially crippling problems in linking research advances made in what previously have been relatively distinct segments of the U.S. R&D system.

Despite the fact that virtually every plant extract commodity discussed would require a combination of public and private research, none of the papers, with the partial exception of Farnsworth and Loub, make explicit recommendations about how public and private funds and institutions should be combined to advance the plant extract industries. Also, I am struck by the large amount of basic "agronomic" (including parallel disciplinary work in plant breeding, plant pathology, entomology, and soil science) research that will be required to realize the full potential of the agriculturally related plant extracts such as milkweed, guayule, jojoba, crambe, etc. Related data on potential ecological impacts of commercial scale production of these commodities are also generally lacking in the papers (and in the scientific literature).

The crucial problem for the plant extract industries will be how to leverage public and private funds for R&D in ways that private companies will not be inappropriately subsidized or discouraged from entering the industry. It was noted above that the public nonmilitary R&D sector (especially for publicly funded applied research) faces stagnating or declining budgets (in real terms). Thus, adding significant research responsibilities for a number of nonconventional crops would severely strain the resources of the publicly funded State agricultural experiment station (SAES) and ARS systems. Moreover, the SAES and ARS systems are implicated in what may prove to be severe crises of public confidence; many agricultural research administrators and agricultural experts outside of the system are questioning whether this system is yielding high quality, "cutting-edge" research (21). It is likely that traditional formula funding appropriations for the SAES will stagnate in real terms over the next several decades and that any real increases in agricultural research funds will come in the form of "competitive grants" (which in theory would be available to nonland-grant as well as land-grant researchers). Thus, Congress should strongly consider making plant extracts research a high priority item and make funding available through a competitive grants program administered through USDA. This is not to argue that individual land-grant SAES should not pursue plant extracts-related research from their formula funds. Indeed, such an allocation of funds would be highly desirable. However, it should be recognized that the pressure on the use of these funds from traditional commodity and other clientele groups of the SAES will be increasingly intense as formula funding levels stagnate, and plant extracts "interests," being relatively new and not so entrenched as traditional commodity groups, cannot hope to fare well in this intensified competition for scarce research resources.

Private research funding problems are of a quite different nature. The bulk of privately funded research is conducted in two major sectors: "venture capital" (or other small) firms and large multiproduct transnational companies. The venture capital sector has several advantages and disadvantages as a locus for plant extract research. On one hand, venture capital firms tend to be more risk-taking in their approach and typically are able to attract high-quality scientific talent because their working conditions by comparison with large corporations are more similar to those of a university. At the same time, venture capital firm research tends to be volatile, as it depends on the continued faith of venture capitalist investors; redundant, as several venture capital firms pursue similar research topics; and short term, since venture capital firms must "strike it rich" with immediate discoveries in order to survive beyond the initial period of venture capital funding. Moreover, most venture capital firms tend to have a "high-tech" bias—i.e., they are typically oriented toward highly advanced technologies which lead to valuable patents. Finally, most venture capital firms are too small to be effective in industrial scale-up.

The R&D systems of large transnationals generally tend to be more stable than those of venture capital firms because long-term funding is secure.

However, large firms' R&D tend to be relatively conservative and focused on differentiation of current product lines. Innovative research in areas such as plant extracts frequently promises to threaten existing product lines. For example, a large agrochemical firm may be reluctant to explore plant-derived biocides, since these biocides might cut into the sales of existing product lines and create research information that could lead competitors to provide substitutes for their products.

Evidence presented in several of the workshop papers and other literature suggests that private sector plant extracts research would be more likely to occur in the small or venture capital firm sector than in the transnational sector. The following comments, therefore, will focus on ways in which research results generated in public SAES/ARS and private venture capital institutions can be coordinated to develop plant extracts industries. One of the limitations in examining this issue is that the workshop papers contain little information on which types of research will be privately profitable (and hence attractive for the private sector) and which will not (and hence needed to be conducted by the public sector or be publicly funded and contracted out to private firms). Thus, were Congress to be asked to enact legislation encouraging plant extracts industries, the aspects of plant extracts R&D that will be profitable to private firms to conduct and those that will require public subsidies should be determined.

As indicated earlier, publicly funded "front-end" research to stimulate private interest in the potentials of plant extract production probably will be needed. Some of this research may be expected to come from existing allocations within the SAES/ARS systems, but Congress may also need to consider a competitive grants program in the plant extracts area to allocate adequate research resources to these problems.

The private research organizations should not be solely responsible for research which is perceived to be privately profitable; the plant extracts industry as a whole may suffer if crucial patents become dominated by single firms. Public institutions should not avoid sponsoring research in areas that are attractive to private firms, since retaining certain crucial discoveries in the public domain may be essential to allow more than one firm to enter an industry. Nevertheless, it should be recognized that the bulk of the "industrial-level" research in plant extracts (e.g., fractionation processes, byproduct utilization) can and should be confined primarily to the private sector.

Plant extracts R&D will by necessity confront two issues that have assumed general importance in U.S. nonmilitary R&D. The first is the relationship between public and private research. During the past several years the U.S. R&D system has been in flux over the "proper" roles for public and private research. The mix of public and private research is now a major issue on many campuses (6) and in State and Federal Governments. It is recognized that public research should be coordinated more closely with the technical needs of industry, especially given the intense international technological competition that emerged during the late 1970's and early 1980's. However, there remains a great deal of uneasiness about how corporate influence on academic research priorities and procedures (especially control over the content of research and over patenting and licensing) will reduce academic freedom, stifle scholarly communication, and deflect research attention from projects that are of little interest to private firms but might be important to long-term public interest. The second current issue within which plant extracts will be implicated is the desirability of patenting life forms (and the corollary provisions of varietal protection offered by the Plant Variety Protection Act of 1970). On one hand, protection of proprietary interests in developing new varieties and life forms will encourage private sector research in these areas and reduce the level of public funding required to stimulate the agricultural and chemical-pharmaceutical industries. On the other hand, protection of new varieties and novel life forms raises certain ethical questions and may serve to deter public R&D in this area and keep useful plant varieties out of the public sector. It is useful to keep these issues in mind when formulating policy to encourage the plant extracts industries and to anticipate possible problems before they develop.

The Organization of Primary Production

This section will comment in general fashion on the papers, especially those by Telek, Wildman, and Tankersley and Wheaton, which discuss plant extracts processes requiring significant field crop production. The main concern will be how the primary production (or "farming") segment of these industries will be organized and the effects of these organizational structures.

The papers under review give virtually no information on how the primary production segment of the plant extracts industries will be organized. In most cases this neglect is understandable; adequate information is unavailable and/or outside the author's area of expertise. Nevertheless, in exploring the potential of developing particular plant extracts, greater attention should be given to anticipating the socioeconomic structures and consequences that would result in the primary production area.

One crucial aspect of the organizational structure of the plant extract industries will be land availability. Land assembly arrangements will differ according to whether the land involved is owned by or leased to farmers and is cultivated. For lands owned or otherwise operated by farmers and currently under production, the crucial issue is: How will operators of these lands be induced to shift their uses of land? For land not under production, especially land not owned or controlled by farmers, the most important question concerns how these lands can enter agricultural production and, if necessary, undergo a transfer of ownership and control into the hands of farmers.

Inducing shifts of land from one agricultural use to another is basically a straightforward economic question. Commodity prices will have to be competitive with those of other crops, and mechanisms will be required to reduce the producer's risk. Newly developed crops can be competitive in the short run with traditional crops if an extract or product from the new crop is introduced as a "specialty" item. This high-value extract becomes a vector for greater long-term development of the crop for that and other products. By capitalizing on a novel or specialty item, the crop can be grown in restricted quantities for favorable prices, ensuring adequate and predictable returns for farmers and providing them with experience in growing the commodity and the opportunity to iron out production problems (e.g., tillage practices, pest control, variety selection). Initiating production of a new agricultural commodity in this way will provide the time necessary to complete further agronomic research and research in industrial engineering or byproduct use that will be critical to the long-term development of the industry. Nevertheless, incentives may be required to encourage farmers to shift their agricultural land from one crop to another, and contracting for guaranteed commodity prices or guaranteed returns may be an essential incentive necessary to effect this crop shift.

One question that may warrant attention in future technology assessments of plant extracts is the possible impacts of growing new agricultural crops on the production of other commodities such as wheat or sorghum and on the communities in which these new crops are grown. Generally, I suspect that the impacts on production levels of conventional crops would not be substantial or undesirable. Most field crop production in the United States has a large geographical range so that regionally confined shifts in cropping patterns would not greatly reduce the supply of other commodities. Perhaps more crucial might be "boomtown" effects of rapid growth and possible subsequent decline of the on-farm and off-farm segments of a plant extract process. Sociological attention recently has been focused on dislocating community-level impacts of boomtowns, both on the "upcycle" and on the "downcycle." In the upcycle, rapid increases in employment and population stretch public services to their breaking point, result in influxes of "outsiders," place pressure on and result in inflation in the value of housing stock, economically marginalize segments of long-term residents (especially the elderly), etc. (25). The dislocating effects of the ("ghost town") downcycle are obvious—deflation of asset values, loss of tax base, high unemployment, and so on. Thus, attention should be given to situations in which the development of plant extracts industries, particularly in what are now sparsely populated rural areas, might lead to a boomtown syndrome.

Earlier I alluded to several problems resulting from shifts of land into plant extracts agriculture. Unfortunately, our research and data base on land ownership in the United States are so inadequate that we lack sufficient profiles on the persons who own farmland that is not in farms and on the motivations for these ownership patterns. The scanty literature on this topic indicates that most of these lands are owned for esthetic and land speculation reasons and would not be shifted into agricultural production easily. One mechanism for shifting public lands, especially in the semiarid West, would be leasing these public lands for an indefinite period or perhaps selling them to farmers after a period of time. In sum, existing knowledge on the possible mechanisms for assembling land not currently in farms is highly inadequate for policy purposes. Identifying underused publicly owned lands in certain parts of the country for plant extracts purposes may be the most satisfactory short-term solution to the land assembly problem.

In addition to the neglect of land assembly issues, the workshop papers ignored the question of whether expanded agricultural production of plant extracts feedstocks will reinforce or undermine family forms of agricultural production. Several key types of data will be required to address this issue. First, and most important, we need information on expected economies of scale in production, since one may assume that commodities for which there are substantial economies of scale will tend to be produced under large-scale "corporate" or "industrial" conditions. Second, information is needed on the amounts and types of labor required for production; for example, commodities that require large amounts of unskilled, cheap labor can be expected to be produced under nonfamily arrangements. Third, data are required on the capital-intensity of production (since highly capital-intensive production techniques tend to be biased against family farming units).

It can be argued that there will be social (especially community-level) benefits to the degree to which agricultural production can be undertaken by family (as opposed to industrial scale) producers (2,22). This is the case where the agricultural production process can be conducted without using a low-wage labor force, since a poorly remunerated labor force tends to have low purchasing power vis-a-vis local businesses. Where possible, the establishment of plant extract-related agricultural production should encourage family forms of production, and R&D should be oriented toward minimizing the barriers (such as high capital-intensity) to family farming units entering this area of production.

Organization of Nonfarm Plant Extracts Industries

For plant extracts industries to reach their full potential, R&D and pilot operations will have to be scaled up into commercial sized facilities. Scale-up involves both technical engineering and socioeconomic aspects. Chief among the socioeconomic aspects are the organizational routes to increased scale and the corollary processes of capital assembly. The scale-up process typically involves one of three major routes. The first route is for a small firm to pioneer in a pilot project, nurture the new technology, prosper, and acquire the capital necessary to become a large firm. The second route is for a small pioneering firm to sell out to a larger firm because of asset appreciation or lack of capital necessary to achieve the next level or stage of scale-up. The third route is for the technology to be developed within a large firm and for the large firm to undertake the investments involved in commercial scale up. The plant extracts industries no doubt will exhibit a variety of paths to commercial scale-up, probably involving all three routes.

The most crucial problem for development of the plant extracts industries is not the route followed for commercial scale, but whether the process will become stalled before the commercial scale-up occurs. As suggested earlier, smaller firms can be expected to be most innovative with regard to industrial processes such as plant extracts. However, these firms tend to have fragile financial bases and may lack the engineering expertise necessary to develop a plant extracts process beyond pilot scale. Larger firms tend to have greater industrial engineering expertise but may not be attracted to industrial production activities that lack secure patent protection or compete with existing product lines.

One of the major types of data necessary to judge the future of plant extracts industries—the likely degree of economies of scale and lumpiness of investments—generally was absent in the workshop papers under review. These data would help policymakers anticipate the likely route to commercial scale-up and the problems that might emerge during the process of industrial maturation.

A final comment I would like to make about the organization of the nonfarm plant extracts industry is to provide a general observation about patterns of industrial innovation in other advanced industrial societies. The problems involved in nurturing new industries are by no means unique to the United States. However, it can be observed that the United States has become one of the most traditional societies in recent years in reorganizing industry and fostering new industries. Virtually all other advanced industrial societies are experimenting with State-private corporations, or other "mixed" enterprises or forms of State-corporate cooperation, as means to achieve industrial policy goals. For example, the Japanese, through their Ministry of International Trade and Industry, are carefully aiming public R&D funds at selected industries for the explicit purpose of stimulating industrial innovation and gaining national advantage over other international trade rivals (especially the United States). More overt patterns of public-private cooperation and State-private industrial partnerships have occurred in France (3). Even the United Kingdom, under the conservative Thatcher regime, has initiated a number of State-owned corporations, in conjunction with private investments, in areas such as biotechnology and biomedical technology. The United States thus virtually stands alone in its laissez-faire posture toward industrial reorganization, and a growing number of analysts have suggested that this laissez-faire posture will result in U.S. industry being outcompeted by foreign firms which have the force of government finance, R&D, and diplomacy at their disposal (14).

The implication with regard to plant extracts is that Congress may need to consider what now are regarded in the U.S. as novel forms of government-industry cooperation to nurture new industries in the long-term public interest. Partially government-owned firms need not, of course, remain publicly owned for an extended period of time; these firms may be sold to private investors after they become sufficiently established and profitable and hence attractive to private firms. Nevertheless, U.S. policymakers may need to reexamine their orientation toward industrial policy and make judicious use of public sector financial, R&D, and organizational resources to nurture new industries such as plant extracts.

Policy and Political Issues

This final section explores some selected public policy and larger political issues that were raised in several of the papers, especially that by Tankersley and Wheaton, and in the OTA workshop discussions. The first such issue involves the connection between an emerging plant extracts industry and the level of Federal commodity programs for basic grains and other agricultural commodities. Agricultural diversification implied by a growing plant extracts industry would expand markets and reduce the need for increasingly expensive commodity programs. To the degree that U.S. agriculture (especially in the Great Plains and Midwest) becomes increasingly specialized in the production of a handful of feedgrains, foodgrains, and oilseeds—much of which is destined for export—the agricultural sector will face price and income instability and may need commodity price supports and deficiency payments. Agricultural diversification will reduce the supply of these grains and oilseeds that have been chronically overproduced and reduce government expenditures for mitigating economic dislocation in the farm sector.

At the same time that one might argue that agricultural diversification will reduce commodity program expenditures, one should urge caution in drastically modifying these programs. Reduction of the scope of these programs will be a relatively long process. Commodity groups that are advantaged by Federal commodity programs can be expected to protect their prerogatives for an extended period of time. One should be aware of the extended time frame over which agricultural diversification will occur and of the underlying reasons why these commodity programs were enacted and why they will be needed some time into the future.

The role of commodity programs has been cast into sharp relief during the present farm recession. Without government intervention, the agricultural recession would have resulted in more dramatic dislocations among farmers. For example, in most areas of the country farmland prices have already declined by about 15 percent. As asset values decrease, farmers' collateral for loans shrinks and bankers may be forced to foreclose on farmers for whom current losses overwhelm equity in farm assets. Federal commodity programs are thus a necessary evil to prevent a severe depreciation in the value of farm assets and to prevent massive farm foreclosures.

In summary, there are several interrelated arguments about farm commodity programs. First, a time of farm recession is not propitious for the initiation of public policies to reduce commodity program payments. Second, there probably will be some continuing need for price and/or income supports for basic foodgrains, feedgrains, and other commodities which are characterized by low price and income elasticities of demand and, hence, by price and income volatility for farmers. Third, it would be politically unrealistic to suggest that farm commodity programs can be dramatically curtailed, especially in the very near future, over the objection of powerful commodity organizations. Fourth, agricultural diversification, such as through encouragement of plant extracts industries, will, in the long run, reduce the need for and expenditures on traditional agricultural commodity programs.

A second policy/political issue of concern to plant extracts is a short cautionary note with regard to the geopolitical implications of nurturing these industries. It is becoming increasingly apparent that foreign trade issues are not matters of mere abstract economic forces. Foreign trade is becoming increasingly central to the economic health of all advanced industrial societies which must be increasingly concerned about the international competitiveness of their industries and about their foreign trade balances. Import substitution is, in a sense, a form of import protectionism—albeit a much more benign form than increased import duties or import quotas—and Federal policymakers will need to be cautious about the geopolitical problems that could result from government support of import substitution efforts.

A final policy issue is that Congress should recognize that some plant extracts processes have more potential than others and that public support should be given selectively and carefully. To illustrate, I would like to use the example of protein from tobacco (Wildman). I do not wish to imply that this process is without merit or undeserving of public support; however, I feel there are certain key problems with the development of such an industry that were not adequately addressed in the paper by Wildman. First, as brought out in the OTA discussion, there are public acceptability problems associated with food uses of tobacco. Second, and perhaps more important, there are market problems with any type of vegetable protein for human consumption, as has been made dramatically apparent during the past 10 years of initiatives to market soy protein as a substitute for meat. Soy protein had great promise; nutritionally, the product was quite adequate, and soy protein promised to widen greatly access to high-quality protein because it was cheaper than meat. However, in a global marketing sense, soy protein essentially failed for one simple reason: There are two types of people in the world—those who can afford any type of protein and those who cannot—and those persons who can afford protein greatly prefer to buy it in the form of meat. Thus, the great promise of protein for humans from tobacco may take a long time to be realized. LPC protein for animal feed may thus have greater short- to medium-term potential than human food protein from tobacco. This example illustrates that the actual market potential of a plant extracts commodity may be less than it appears on the surface. Policymakers will have to acquire more detailed social science and marketing information on many plant extracts commodities to determine more accurately their market potential.

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PLANTS: THE POTENTIALS FOR EXTRACTING PROTEIN, MEDICINES, AND OTHER USEFUL CHEMICALS

(A Review of the OTA Workshop Papers)

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An Alternate Use for Tobacco Agriculture: Proteins for Food Plus a Safer Smoking Material

by Samuel Wildman

The technology for extracting leaf protein has more important societal implications than the use of tobacco for protein. There are many reasons why tobacco leaf protein would be unacceptable in scarce resource situations such as in developing areas. The enormous amount of nitrogen fertilizer needed to produce tobacco protein is expensive and would be prohibitive in developing countries where imports of chemical fertilizers require the use of foreign exchange. A cost comparison of producing regular tobacco and producing tobacco for leaf protein on a per-acre basis is needed to judge the potential costs to the farmer. Because leaf attractiveness is not so important for tobacco grown for protein extraction, pesticide inputs would be less than in conventional production. The higher input costs accrued through four annual cuttings, each requiring fertilization, must be weighed against a higher value product. These tradeoffs must be examined in greater depth.

This technology is biased toward resource advantaged U.S. farmers because this kind of tobacco production is capital intensive in its use of nitrogen fertilizer and harvesting machinery. Resource disadvantaged farmers, particularly the small allotment holders in the rural South, would become even less competitive with the larger farmers, ultimately becoming more reliant on subsidies and less able to survive in a free market situation. Although the allotment system for tobacco may be a disadvantage to the ultimate rationality of farming in the South, by maintaining small farmers on the land, it has had important social benefits. A move to tobacco leaf protein may counteract that social welfare by shifting resources from less advantaged to more advantaged farmers.

The sociological problem of integrating an innovative structure of production into an ongoing technological system seems to be the biggest constraint faced by the tobacco protein project. The unique mechanism of physically and chemically fractionating the leaf and extracting Fraction 1 protein appears to be an important breakthrough that could be used for a variety of plants besides tobacco. Other plants may not have the established allotment structure and the established growers network of tobacco, but their products might be more readily accepted by the public. A nitrogen-fixing plant seems more appropriate because it would require lower fertilizer inputs.

Once the leaf protein is produced, there are marketing and market penetration problems that are difficult for small entrepreneurs to overcome. The medical market for leaf protein seems logical, but it is small, not particularly lucrative, and unlikely to support the large investment needed for protein extraction. The other products that the leaf protein might replace, such as egg albumin, are not in short supply. For example, the poultry industry is well developed. There would have to be a large price incentive for industries to seek a new product as a substitute to egg albumin in food processing. A substitution would require some production shifts in tooling or processing, and food industries seem particularly unwilling to make such shifts.

One argument of the large food manufacturers against the new product is that leaf protein from tobacco would prompt consumer groups to launch antinicotine campaigns. Possible problems arising with labeling—consumer acceptance of a product labeled as containing tobacco protein—may compound the difficulties facing tobacco leaf protein.

An alternative crop for this technology was not explored by Leaf Proteins, Inc. Soybeans or peanut leaves might be good substitutes in the South. Because they are nitrogen fixers, they require less fertilizer, therefore reducing crop costs and possibly increasing the profit per hectare. Initial profitability for the grower and producer of a vegetable protein product would have to be highly subsidized by State and Federal Governments. The commodity focus of U.S. agricultural development has limited the development of new crops, and subsidies to tobacco allotments inhibits the potential competitiveness of alternative crops.

The potential for local production must be determined when considering leaf protein as a dietary supplement for developing countries. As most developing countries have limited foreign exchange and are in a high debt squeeze, most protein for human consumption must be processed locally. The protein extraction process might be appropriate in developing countries where the State sector is active and will subsidize some of the initial start-up costs. In these countries, it is unlikely that tobacco would be the crop chosen for leaf protein extraction, however, except perhaps in the People's Republic of China, which already grows a great deal of tobacco.

In countries producing sugar, which has low current and expected world market prices, the sugarcane grinders and centrifuges might be modified for leaf protein extraction. However, the cost of machinery conversion probably would have to be borne by the State, and establishing distribution channels at first would have to be underwritten through grants and soft loans. It is doubtful that the protein could ever be self-supporting in poverty-stricken markets; it would have to be instigated as a social welfare measure.

The dehydrated alfalfa process provides an example of leaf protein extraction in the United States. It would be instructive to look at the problems of Pro-Xan processing and marketing.

If leaf protein were to be extracted from tobacco or other crops, plant breeders would have to reorient their breeding thrust. For example, if one were to use soybeans, one would stop breeding primarily for bean quality and also emphasize increased leaf mass and protein content. Bringing about a shift in breeder ideology might be a problem. Reputations in tobacco breeding sometimes have been made on a leaf appearance rather than foliage density.

The use of this new product would have to be linked closely to its manufacture. At first the process might be vertically integrated from contract growing to manufacturing, particularly if a new variety of tobacco or soybean were used. Once the new crop is established, contract growing probably would cease because it would be more profitable for the food manufacturer to buy on the open market.

In Third World countries, the use of tobacco instead of soybeans or another nitrogen-fixing food crop as a source of protein would have to be considered carefully. Alternatives to tobacco should be sought. Efforts are in progress to breed a tropical soybean that could be grown in areas where tobacco now is grown. The advantages of extracting protein from soybeans or peanuts instead of tobacco is that soybean and peanuts are nitrogen fixers, and the beans can be used directly as food or as a source of marketable oils. One criterion for choosing plants for protein extraction is that the plant or combination of plants provide leaves for a good portion of the year to avoid the costs of supporting idle machinery and the negative effects of a seasonal labor force.

For leaf protein to be a solution to Third World food problems, it would have to be produced locally at low cost. Available machinery should be adapted to avoid debts incurred for importing processing plants. Protein production would not generate foreign exchange because money from local sales cannot be used to repay most loans, and leaf protein produced in Third World countries probably would not be sold on an international market.

Leaf Protein Extraction From Tropical Plants

by Lehel Telek

Telek's discussion is aimed primarily at Third World countries. The process he reports is considerably simpler and cheaper than that suggested by Wildman. Telek's system of extraction deals with protein for animal fodder instead of the higher priced human food market. This process might be adapted to cooperatives, organized communities, or sugar refineries which, as protein extraction factories, could use their equipment and labor more economically year round.

This method of leaf protein processing is best suited for a relatively large, integrated operation of animals and plants. In the Third World, the ideal 10-cow/hundred-hog production unit is that of a wealthy farmer. Small peasant farmers have too few animals to apply the process effectively. Further, in most developing countries, few people eat animal protein, so the emphasis on fodder for larger animal herds will have little impact on the poor, landless worker or semiproletarianized peasant in most of the Third World. The process seems best adapted to centrally planned economies or cooperative production units.

Using a tractor as an energy source greatly limits the type of farmers for which such technology might be attractive. The price of tractors leaves few peasant farmers the option of this technology. In the Third World, as in the United States, large scale animal production now tends to be based on purchasing feed inputs rather than producing them on the farm.

Leaf protein extraction might encourage more integrated farming enterprises, which raise livestock and produce livestock feed on the same farm. This would require a high level of planning and coordination, and probably is most appropriate for either the public sector or highly capitalized, management-intensive private entities, such as companies producing beef for export. However, these entities would be more likely to supplement foreign exchange earnings and not directly increase protein availability to the poor in these countries.

The leaf protein technology described by Mr. Telek seems more adaptable to U.S. farming situations, particularly farms where rising costs of inputs encourage self sufficiency. This technology seems particularly appropriate for integrated dairy operations that might be expanded to include some hogs. The Cooperative Extension Service might work with small implement dealers to introduce this technology. The current crisis in farm incomes encourages adoption of such low-cost machinery.

There is a danger in depending on protein supplement programs to solve the problems of malnutrition in developing countries. These programs, particularly when imposed from the outside, often serve to only temporarily deal with the symptoms and not the causes of poverty. A community-controlled food supplement program that allows the community to produce protein and distribute it to children would be more successful in decreasing the number of malnourished children. More data on cost of production are needed. In addition, alternatives within the farming system should be examined to determine which ways of producing supplemental proteins—meat produced with LPC, LPC for human consumption, or alternative sources such as eggs from a community chicken-raising project—are more in keeping with both nutritional habits and production possibilities.

Molluscicidal and Other Economic Potentials of Endod

by Aklilu Lemma

The development of endod is a good example of the potential of plants for community-controlled solutions to community problems. Research on the basic chemical properties of endod indicates its potential to supply a low technology molluscicide to control schistosomiasis. A similar community-based program could be envisioned in countries where malaria is a problem, since the endod berries have larvicidal properties effective against the mosquito.

Endod seems to grow wild under a variety of conditions. Cultivating endod and introducing it into new areas requires better knowledge of the plant's climate and soil requirements for optimal growth.

A community controlled program could be based on intensive endod cultivation by the public or private sector and treatment of infection sites with endod applied by the community. In a community-based project concerning public health problems, the public sector would have to bear the start up and research costs, and the community should be able to keep the project going through its local tax base and volunteer participation. The public sector would also have to be active in the educational campaign to link the community's actions to the results obtained, thus encouraging long-term local support and participation in the project. A monitoring system to gather statistics on the health impact of such a program, such as decreased infant death and disease incidence, would be beneficial. Unless communities perceive schistosomiasis as a problem and endod as a solution, continued community participation in possible future programs using endod as a molluscocide is unlikely.

Because research and start-up costs for community-based disease control programs are substantial, development assistance from more affluent countries may be needed. The crossover of benefits may be substantial so that the donor countries benefit at the same time as providing assistance. For example, mosquito control is a huge problem in many areas of the United States where DDT is outlawed. Endod could be an effective larvicide for mosquito control in such areas as rice fields in the central valleys of California where the mosquito is a consistent social irritant. Another possible application for endod is control of crayfish which dig holes in the dikes of rice paddies in California. Endod properly applied could reduce the costs of crayfish control and environmental problems of pesticide run-offs.

Endod research has progressed because of the combined efforts of the private and public sectors. Continued public sector support is necessary. The participation of the United States in endod research could both help alleviate Third World problems and have payoffs at home by providing inexpensive, environmentally satisfactory biocides.

The Role of the Alkaloids of *Catharanthus Roseus* . . . .

by Gordon Svoboda

Gordon Svoboda's remarkable presentation on the development of anti-cancer alkaloids from the Madagascar periwinkle should be considered in a larger context. A major pharmaceutical company, in this case Eli Lily, had to have available capital and be willing to risk it on such a "fishing expedition."

While the initial discovery was made at a university at public expense, product development was done by private enterprise. This link between basic university research and applied industry research seems to be an economically and socially beneficial model that should be encouraged. This case study appears to be unique, as no pharmaceutical company is doing botanic pharmaceutical research. It is important to understand why this research has been discontinued, especially since Dr. Svoboda's research apparently has been very profitable to Eli Lilly.

Has research shifted from botanical to chemical pharmaceuticals because chemical research can be carried out more rapidly than botanical research? Or, is industrial research funding being reduced in general, and, if so, what public efforts can counteract that situation? One important thing to look at is the potential linkage of university-based botanical pharmaceutical research and industry application. While the unversity should not be a tool of industry, it is important that top researchers continue screening, the results from which could be useful to pharmaceutical company scientists for subsequent product development research.

Part of this process involves an availability to both public and private sectors of past screening results to indicate which botanicals are worth product development efforts. The screening program and linkage of this program to potential users require more study. The users, including private entities, must perceive that information on results of screening is available, and preferably computer accessible.

The difficulty synthesizing these anticancer drugs demonstrates that botanicals and their biological sources have a continuing place in medicine. Despite the large number of leaves necessary to produce a small amount of the anticancer drug, a relatively small acreage is required for agricultural production. However, since growing probably would be done under contract arrangements, with production agreements between private farmers and pharmaceutical companies, it might provide price stability and a steady income for farmers who otherwise might depend on a single commodity. More information is needed on these kinds of agreements and variations in contract farming systems. When vertical integration is too intense and the market is oversaturated, as in the broiler industry, exploitation of the contract producer occurs, but when contracts are let simply to provide the input necessary for an established industry, a more equitable arrangement can be reached between the producer and the contractor.

Marine Plants: A Unique and Unexplored Resource

by William Fenical

Marine sources of food, pharmaceuticals, pesticides, and industrial chemical feedstocks have great commercial potential and may have much less negative impact than land-based botanicals. Although research seems to have been on the taxonomy of marine organisms rather than their commercial potential, and only limited biochemical screening of marine plants for possible commercial products has been done, there are a number of interesting marine plant constituents that might be valuable.

The one marine plant industry that has developed in the United States, that of extracting agar, carageenan, and alginate from seaweeds, seems to be highly mechanized. It is difficult to conceive that this technology would be available to any but the largest multinational corporations. While certain algae cultivation is labor intensive in Japan, it is highly unlikely to be so in the United States. Thus, economic benefits derived from marine research would not necessarily accrue to small producers.

It appears that the public sector is not interested in or prepared to undertake marine-based pharmaceutical research or screening in the near future, but it is very important that these species be preserved until such time as they might prove useful. Insomuch as pollution can radically alter the nature of coastal habitats and their organisms, a critical government role would be to ensure that the oceans, particularly coastal areas, are kept as free as possible from pollutants. The recent deregulation of industrial waste dumping into major oceans may alter marine populations and ultimately decrease some sources of genetic variability. Perhaps we may decide not to do the expensive research and development necessary to develop marine products now, but we should not limit our future chances to do so by unregulated pollution of the oceans.

Insecticides, Insect Repellants, and Attractants From Arid/Semiarid Land Plants

by Martin Jacobson

This paper points out that many useful insecticides are available from plants. One wonders why, if nicotine is an effective insecticide as indicated by Jacobson, the work on tobacco does not consider nicotine as an insecticide as well as a source of protein and cigarette fiber.

The work at USDA, Beltsville, on isolating and identifying insect feeding deterrents in various weeds and crop plants might provide alternative crops for farmers if appropriate processing and marketing structures were developed. Putting these structures in place clearly would require government assistance, but ultimately might provide low cost, more environmentally safe insecticides that substantially could reduce the cost of crop production in the United States. These products also might have an impact in Third World countries if they can be produced with appropriate technology and little imported machinery. Some economies of scale probably would give a slight advantage to larger units of production over smaller peasant plots.

The work done by USDA at Beltsville in identifying potentially useful insecticidal plants must be taken one step further—to production. Private and public sector research to determine commerical feasibility and establish marketing structures is the next order of business.

Jacobson considers the neem tree to have the most potential as a source of insecticides. More agronomic information is needed to understand the neem growth cycle and the scale on which neem should be cultivated. The preliminary evidence suggests that neem could be a suitable cash crop for small family farms and that processing need not be done on a large scale. However, more work on scale of cultivation and process and economic feasibility must be done and questions on labor and product distribution answered. For example, how much local employment can neem seed processing generate? How much will this new industrial or semi-industrial development depend on established transportation networks to distribute the insecticide products? How large would a neem plantation have to be in order to be commercially feasible? How does the harvest cycle relate to other small farm labor demands?

The 5-year waiting time for the neem tree to bear fruit necessitates that any project introducing neem, especially projects in developing countries with small farmers, must ensure that sources of food and cash are available to the farm family for the first 5 years. The problem of motivating farm families to invest time, energy, and money in long-term payoff crops has to be examined when considering neem for commercial development in Third World countries.

Processing and cultivation have to be linked to markets from the beginning. The work already under way on neem suggests that an appropriate next step would be continued government support linked with small scale private industry for processing and marketing the product.

In the United States, public lands or communally held lands, such as those of the American Indians, seem prime targets for planting neem trees. However, labor requirements for harvest should be examined seriously. How is harvesting done, how many people must be involved, and how soon after ripening must the seeds be harvested and processed? The frost susceptability of the neem tree might limit its use in Southwestern United States. The possibilities for selective breeding or simply selection for cold resistant species might be investigated. Land grant universities and small farmers could be involved in this screening procedure.

Other important questions that must be examined in regard to developing country production of the plants mentioned by Jacobson are those of labor requirements and distribution of labor among different family members. Labor intensity at certain times of the year may exclude small farmers, who often are limited by labor availability, especially at peak harvest times, from growing particular crops. Crops that are labor intensive, but have labor requirements more evenly distributed throughout the year, may be more appropriate for small farms. For example, basil might be a good cash crop for farm women. A marketing system would have to be developed and linked to industry, perhaps a small scale community-based industry specializing in oil from the basil plants.

Multiple product species, such as the mammy-apple which yields an insecticide, wood, and fruit, have potential for increasing local self-sufficiency in developing countries. Systematic research on processing requirements of such multipurpose crops is needed. At this point, a good strategy might be for communities to work on developing an industry where there would be local supply of the raw inputs and local consumption of the outputs. It would be necessary to link community and industrial capital interested in investing in up-scaling the extraction procedure.

One of the important aspects in all of these crops is that apparently a substantial amount of plant biomass is required to yield a commercially viable amount of the product. This suggests that simple, decentralized plants, using village labor and village management which would increase the potential for community control and regional self-sufficiency, would be the best way to develop these products. That would require working with local communities at an early stage in the commercial development of these crops.

Chemicals From Arid/Semiarid Land Plants: Whole Plant Use of Milkweeds

by Robert Adams

The use of arid and semiarid land plants as sources of industrial chemical products is appealing. The Jacobson and Adams papers illustrate that many of the common plants in arid and semiarid areas have potential for product development. The economic feasibility of cultivating these products on rangeland or on lands in other dryland crops or under irrigation, and subsequently developing the products, should be examined. Guayule and jojoba, which already are cultivated in certain areas of the United States, will be important models for arid/semiarid land plant development.

Developing cultivation techniques for arid and semiarid land plants and fulfilling labor requirements need attention. Certainly there is a great need for a dryland crop to replace irrigated agriculture in Oklahoma, Nebraska, and western Kansas. However, such crops will be adopted only when markets for them are established. Crops requiring a high level of processing, such as milkweed, will be less readily accepted than crops requiring minimum processing.

Milkweed development is such that large-scale production probably is needed to make it economically viable. Large amounts of milkweed are necessary to produce relatively small amounts of the more valuable products. The ability of a small, locally based industry to establish a milkweed stand and develop the variety of markets necessary to make milkweed financially viable is questionable. Scaling-up milkweed processing to make it commercially viable perhaps is the greatest constraint. Private enterprise may not be willing to take the risk, and capital available for small-scale venture activities, even in local communities, is scarce. Processing must be developed at the same time as milkweed is being produced. Timing the different aspects of production is crucial.

The toxicity of milkweed is a problem because the plants must be processed before use and the chance of spoilage during storage is increased. Milkweed's profitability and, thus, competitiveness with dryland wheat depends on inositol and pectin, two products that are difficult to extract and purify. Since these are high cost/low demand products, a balance must be found between the amount of milkweed needed to make the processing plant economically viable and the amount needed to supply, yet not flood, the inositol and pectin markets.

Introducing milkweed as a monoculture would tend to favor vertically integrated companies, large scale farmers, and rental land tenure arrangements. More information is needed on the use of milkweed as a livestock feed and its degree of competitiveness with feed corn, silage, and grain sorghum. Vertical integration from cultivation of milkweed to processing would be necessary and farmers have to have an assured market for milkweed.

A large amount of investment, probably from the public sector, will be necessary before milkweed can become a viable choice for U.S. farmers. The high degree of processing probably will preclude its use as a crop in Third World countries. Milkweed must be examined in comparison with alternative crops, particularly those crops requiring less processing, before large public investments are made. Unless simple machinery, fewer products, and a tight link between cultivation and processing can be developed simultaneously, it is doubtful that U.S. farmers will benefit from cultivating milkweed.

Strategic and Essential Industrial Materials From Plants—Thesis and Uncertainties

by Howard Tankersley and Richard Wheaton

This paper raises important issues about the public sector's interaction with farmers producing raw materials and processors processing the materials for national and international markets. Domestic production of strategic materials, which are unavailable or in short supply, would be advantageous to the United States. Because no domestic industry to process these products exists, government support will be crucial. The U.S. Defense Department contract which has supported development of guayule as an alternative to natural rubber is an important example of government support for new crops.

For U.S. industry to be supplied with sufficient quantities of these materials, farmers must be assured of a regular market for their products. Bankers and other lenders must be willing to give long-term credit to farmers investing in new crops that take a long time to establish. Government must work closely with local bankers to guarantee such long-term credit arrangements. Farmers may be motivated to change to strategic crops, particularly grain farmers in dryland areas of the United States, but current lending procedures and debts of the U.S. farm population suggest that without credit advantages such crop shifts are unlikely to take place.

The paper points to the necessity of subsidizing industries to develop these substitutes. However, subsidies for farmers, particularly as credit and applied research, will also be important. The high cost of price supports for the major commodities in the United States suggests the need to move quickly to subsidize alternative crops that ultimately may not need so large government inputs in the future.

Because nonexistent crops have no political power, there is little pressure for government involvement in them. Whereas the consumer would be the ultimate beneficiary of many of these alternative crops, consumers are not well organized pressure groups. It will be important to enlist the assistance of already organized groups whose welfare will be affected to gain political support for these projects. Commodity programs are the outcome of efforts by farmers and their organizations such as the Farm Bureau, Farmers Union, and the National Farmers' Organization. These organizations must be included in the early stage of crop substitution planning to assure that farmers' interests are protected. It might be useful to work with commodity groups, particularly those representing commodities grown in areas where new crops might be developed.

It would be interesting to look at the tax writeoffs available for planting jojoba to see their scope and to whom they apply. Generally the farm family does not profit from farming tax writeoffs and ultimately these kinds of tax subsidies encourage more absentee ownership.

It is important that U.S. foreign policy and U.S. domestic agricultural policy be consistent. Although farmers and USDA are moderately powerful in determining domestic policy, the State Department seems to be able to override their decisions when foreign policy concerns arise.

It takes a long time to develop a new crop. Farmers are disadvantaged because they absorb production risks and often are not paid for the year's production until the end of the growing cycle. Because new crops will take several years to become established, alternative sources of incomes for farmers during this initial period must be sought. Research on alternative crops should include work on intercropping or other mechanisms that can provide a regular income while the crops are being established.

The labor demands for crops such as guayule have not been discussed or evaluated in the Tankersley and Wheaton paper. It is important to see if the introduction of these alternative crops would create a new class of seasonal farm laborers or result in the creation of a smaller, year-round labor force. Alternative crops could help revitalize rural communities, particularly if the processing could be done locally. Will guayule rubber be processed in existing plants? Will intermediate processing take place near the point of production?

To assess alternative crops further, it is important to analyze the vested interests of each crop and its byproducts. For example, the importers of newsprint and paper, which kenaf would displace, may try to influence legislation. The kenaf experiment deserves close attention.

Commerically oriented research clearly is necessary and cooperative efforts between USDA, land grant university scientists, private development firms, and private industrial producers should be considered. Government support of research in all these sectors probably will be required. A dynamic capitalist system requires that the government can assume the risks of production in order to establish a profitable industry. Profit is correctly seen as belonging in the private sector, risk as belonging in the public sector.

It is vital that researchers work not only with farmers but with the end product producers to assure that breeding and selection meet the needs of production. This will help to provide a ready market for what farmers grow. A screening and breeding program for alternative crops would be very beneficial and could help strengthen ties between farm organizations and potential growers and industrial users. Clearly a coordinated government effort in appropriate agencies is needed for supporting R&D that may ultimately make these products commercially viable.

Historically, producing material has been less of a problem than processing the material. Industry seems more rigid than farmers in shifting products and techniques. Industry also seems less willing to take risks than farmers, who are accustomed to risks.

The shift in developing countries away from nonfood export crops might increase the availability of prime land for food production. These countries suffer from enormous balance of payment problems. A shift back to food, particularly if it could be coupled with the use of locally available pesticides and fertilizers in a mixed cropping system, migh[illegible]duce dependence on foreign food imports, increase the foreign exchange balance, and increase the economic and political stability of many of these countries. However, it is important to realize that the international grain trade and the multinational corporations controlling it benefit greatly from this food dependence and from surplus grainstocks in the United States. In the grain trade, as much profit is made from shipping as from the sale of the actual products, and a great price fluctuation caused by a world market instead of a local market increases profits. The grain trade may be a potential opponent of shifting to multiple crops and increasing self-sufficiency, both in the United States and Third World countries.

A shift to food production in Third World countries often benefits small farmers, and might result ultimately in income redistribution both in rural and urban areas. Such a shift would decrease government's desires to subsidize cheap food because soft credit on food imports would no longer provide an artificial underwriting of food costs. That might lead to increased food costs in Third World countries, but those costs might be offset by increased food production and increased income, particularly to rural areas.

Prototype processing plant development should be undertaken as part of substitute crop development. However, such plants should be encouraged as joint government/private sector ventures, rather than simply government prototype plants. The investment of private industry will help increase their commitment to using the plants.

The variety of mechanisms available to the government to discourage imports and subsidize shifts in production needs to be fully examined. The wide variety of tax incentives and disincentives should be looked at before direct tariff protection or import negation is undertaken.

An arid plants experiment station might be called for to develop these products more fully. This experiment station should be staffed with more than agronomists and plant breeders and include people who might apply these products to industrial and nonindustrial uses based in the same area. Private firms might be encouraged to rotate personnel to these experiment stations/pilot plant areas in order to be fully involved in the development process.

The USDA Economic Botany Laboratory's Data Base on Minor Economic Plant Species

by James Duke

The data set of the USDA Economic Botany Laboratory could be valuable for any kind of experiment station breeding, selection or processing program. The case for a wide ranging, well documented data base is made strongly in this paper, and the amount of Federal dollars spent to support the program properly would be justified by the large savings made through information provided by the data base.

The funding for such a data system is important. This system should be on-line and linked to experiment stations throughout the United States. Further, informational linkages should be obtained with CGIAR (Consultative Group on International Agricultural Research) to avoid duplication of basic research and encourage greater use of existing information. A comprehensive, up-to-date, and flexible data base such as the one represented here is essential for organizing and making the vast amount of existing data available to users. One of the problems of the system is that it is little known. Knowledge, use, and support of this system must be expanded.

The potential value of data on ecological amplitudes of pests and diseases is very important for breeding programs. That file could save scientists thousands of hours of work. Millions of dollars for farmers and consumers could be saved if such data were put to use.

Information Gathering and Data Bases That Are Pertinent to the Development of Plant-Derived Drugs

by Norman Farnsworth and William Loub

While Dr. Duke's paper deals with a wide variety of characteristics, Dr. Farnsworth's paper focused on drugs. The same arguments on cost effectiveness of data bases apply to Dr. Farnsworth's paper as apply to Dr. Duke's paper. The potential for avoiding costly mistakes by making both positive and negative research results available are increased by such data bases if they are on-line and available.

That data base would inform both processors and consumers, creating demands that farmers could then fulfill through shifting crop production. One of the crucial issues here for farmers is the difference between monoculture and mixed farming systems. The tendency in the United States has been towards monoculture. While this had certain elements of management and capital efficiency for farmers, it also increases farmers' risks through dependence on single commodities that tend to be overproduced in this country and worldwide. One of the important aspects of alternative crops is not that there will be a single miracle crop that will save the family farm, but that increased diversity available to American farmers will decrease the dependence of U.S. consumers on imported goods, particularly chemical products that will result both in lowered prices and higher quality. This increased diversity for farmers will in turn help U.S. taxpayers by decreasing the bills currently incurred for subsidizing the basic few commodities that are the focus of most U.S. production research.

It is important to remember, however, that those commodities are the basis of U.S. agriculture as we know it today. Alternative crops that can either be alternated or intercropped with our current crops would be an asset. Industrially, looking at crops that can interdigitate with or complement these crops on an industrial basis would also be important. For example, the kinds of botanical pesticides and products that can be used to coat grain for storage and reduce grain storage loss as insecticides might be an important kind of crop to consider in areas of high grain production and storage.

Whereas the use of plants as chemicals seems to have a ready market, health needs are less often translated into products because often the sickest people, as the hungriest people in society, have less effective demand. One of the roles of the government sector is to try systematically to meet the needs of those that are disadvantaged in a variety of ways. An important example of the positive role of the state is pointed out by Dr. Farnsworth. Japan and West Germany are active in the botanical pharmaceutical area. The close link between the public and the private sector in this is crucial for understanding its success.

One of the other issues that has impact on plant development is that of patents and right restrictions affecting ability to make a profit. It is clear that from farmer to processor to marketer, if a profit cannot be made at each step, a new crop or a new product cannot be introduced, whatever its potential large-scale societal benefits.

For this project to be successful, a close partnership with industry must occur. Again, government must act to further that link without creating a monopoly that is disadvantageous to the consumer.

The potential of botanical based medicines seems very high. It is also diversified. There is no one crop that will provide all the answers. This fact alone implies a systematic basic research program that involves careful screening and careful analysis prior to the undertaking of any project. The data bases described by Drs. Duke and Farnsworth seem basic to this process. Research that is government supported must be part of building a cumulative, collective undertaking, even though each discovery of course is that of individual scientists. Individual scientists must be assured access to the data bases so that they can be then implemented in further development. It is crucial that such research be related to potential use and use be related to manufacture and marketing. Government has an important role in establishing and subsidizing such linkages.

Conclusions

1. Research on alternative uses of plants, if combined with applied research on processing and marketing, could be very beneficial for the North American farmer and U.S. taxpayer, and, if the processing were relatively simple, to Third World farm families as well. Such crops would increase the diversity and self-sufficiency of farms and nation-states.

2. Research and development will need strong government involvement, through tax incentives and direct subsidies. Direct subsidies are especially important if less advantaged farmers and firms are to become involved in developing these new crops and products. They should be included not only to encourage better distribution of the benefits of the enterprises but because such units are more likely to make more radical changes because of their relative precarious situation.

3. Labor requirements and location of processing plants need to be assessed carefully. Such diversified crops and industrial processes have a great potential for furthering rural development in the United States and community development in Third World countries. In both cases, local government must be involved. Federal help in making

these links might be the catalyst needed for such development to occur.

4. Educational programs to increase awareness of the potential of new crops should be carried out, perhaps through government supported seminars coordinated through the USDA cooperative extension service. Established interest groups need to be persuaded that new crops or products ultimately will benefit their constituents. Minority entities, such as Indian nations, are particularly important benficiaries of arid land plant development and need to be included as participants in the development of an arid land plant program.

5. Research in this area should continue and be better coordinated. The data systems described need increased support and to be linked to ongoing scientific activity and industrial R&D efforts. Personnel and computer funds must be appropriated in this area. The land grant universities and the USDA should be incorporated early into this research network. Not only will this improve the quality of the research but will ensure that an established lobbying group has a stake in the program.

6. Coordination of government agencies—including the Food and Drug Administration, USDA, Department of Defense, Department of State, and others—is important for the full development of alternative crops. Liaisons should be formed with appropriate agencies.

ECONOMIC PERSPECTIVE OF INTRODUCTION OF NEW CROPS

(A Review of the OTA Workshop Papers)

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Introduction

The commercial development of a new product from a new crop, a new product from a known crop, or a substitute for an established product requires that a system involving three major subsystems be established: production, processing/marketing, and consumption (PMC). Each of these subsystems has a number of functional components, all of which must be in place and operating viably for the system to function effectively.

Historically, work on new crops has concentrated first on production technology, with only a general, and often somewhat vague, vision of the structure and magnitude of demand. Obviously, technological aspects of crop production must be researched, but demand and consequent costs and financial returns are just as critical.

Demand analysis and quantification are difficult to deal with at early stages of product development because there is a lack of data. Early critical input into decisions about making additional R&D or commercial investments can be provided by information gathered from experiences in other countries, similar existing products, and production technology research which will begin to generate some cost component information.

A number of possible economic benefits must accrue at various levels of the PMC system for successful introduction of a new crop/product. Benefits must accrue at the farm level; the marketing/processing level; and, for the government to cooperate in policy and/or R&D resources, at the national economy level. Some possible benefits at these different levels are listed in table 1. Whether a crop becomes profitable or not depends on more than the quantification of economic payout. Figure 1* shows the components of PMC Systems, demonstrating the wide range of possible economic variables involved in a PMC System.

In the past when new crops became commercial, the development of the system relied primarily on entrepreneurship, risk capital, and time. If one looks at crops that have been introduced and subsequently commercially developed in the United States within the last 50 years, one finds that there were one or a few key individuals or institutions who were convinced that the crop had a future and did not give up; for example, it was Mr. A. E. Staley for soybeans (processing); a couple of seed companies for sunflower; USDA and Texas A&M Sorghum Breeders for grain sorghum; and a few California avocado (hobbyists) growers for avocado. These are what we might call "commodity champions."

If new crop research were to follow a more integrated approach, carrying out economic analysis simultaneously with technology research and constraint identification and analysis, profitable crops could be expected to be introduced in less time and at less cost. Demand and profitability analysis for the entire system, not just cost of production and partial product analyses, are needed.

The three following possible types of prefeasibility economic determinations should be made prior to the prototype stage:

1. In the case of import substitution or an alternative crop for an existing product: Is the price of the end product increasing at or above the rate of inflation?
2. Does the product have a high income elasticity of demand—i.e., as consumers' incomes increase do they allocate increasing proportions to that product?
3. Is there self-perpetuating demand for a new type of product—e.g., health foods?

Figure 2, "PMC System Decision Matrix," was developed in the NSF study on "Feasibility of Introducing New Crops" to assist in analyzing the technical, economic, and institutional (regulatory, policy, sociological, etc.) constraints on production, marketing (procurement, processing, distribution), and consumption of new crop products. The matrix provides an idea of the components involved in new crop development, which if analyzed would provide an indication of economic feasibility of the crop/product introduction.

The discipline of economics never has enough data to give unequivocal answers, and economic data are especially limited in the early stages of new crop R&D. One effective technique to get the best possible estimates not only of economic but also technical and institutional feasibility is a modified Delphi technique. The technique gathers fact and opinion from all knowledgeable people about a subject, gives values to the judgments, and eventually arrives at some consensus on the actual situation regarding the issue. By using the Delphi technique to gather information on the various components shown in figure 2, the stage and potential of a crop's commercial development can be identified.

Simulation is one of the more comprehensive eco-

Table 1.—Benefits That Have an Impact on Economic Feasibility of New Crop Introduction

A. Farm Producer Benefits

1. Risk reduction
2. Stress tolerance
3. Value per acre intensification
4. Use of marginal land consistent with environmental limitations
5. Market diversification
6. Improved use of family labor
7. Improved use of permanent hired labor
8. Lower capital input

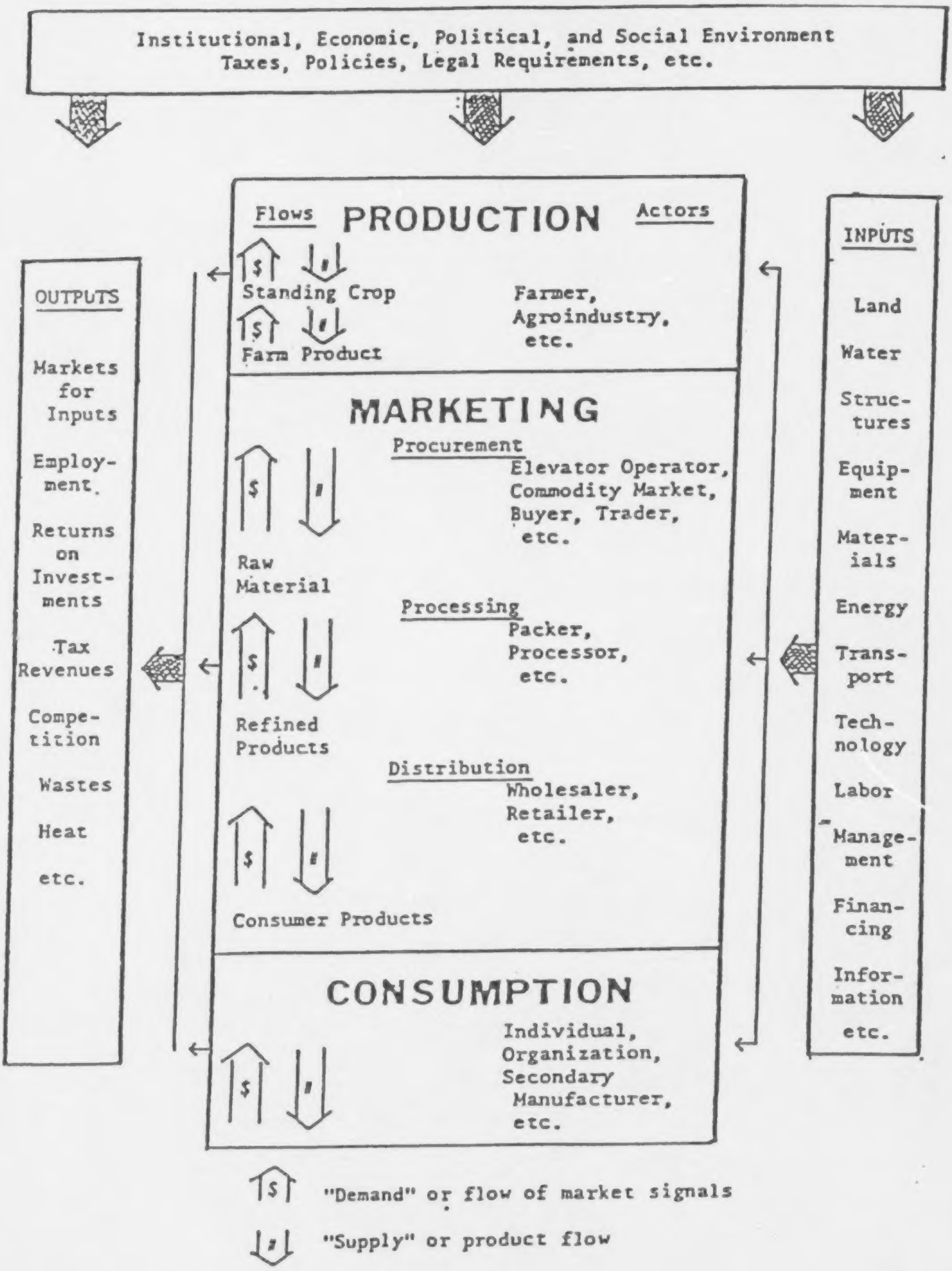
B. Marketing and Processing Benefits

1. High market demand potential
2. Existing installed processing capacity
3. Low processing system cost
4. Consistent demand
5. Product source diversification
6. Supply security enhancement

C. National Economy Benefits

1. Import substitution
2. Export market (foreign exchange earnings)
3. Productive use of otherwise marginal resources
4. Adaptable to natural resource conservation practices
5. Relatively low energy requirement for production and processing
6. Market diversification
7. High potential impact magnitude
8. Impact in areas with limited alternatives
9. Strategic or essential supply security (risk reduction)
10. Employment generation

Figure 1.—General PMC System[a]


Institutional, Economic, Political, and Social Environment
Taxes, Policies, Legal Requirements, etc.
OUTPUTS
Markets for Inputs
Employment
Returns on Investments
Tax Revenues
Competition
Wastes
Heat
etc.
PRODUCTION
Flows
Actors
$
Standing Crop
Farm Product
Farmer, Agroindustry, etc.
MARKETING
Procurement
Elevator Operator, Commodity Market, Buyer, Trader, etc.
Raw Material
Processing
Packer, Processor, etc.
Refined Products
Distribution
Wholesaler, Retailer, etc.
Consumer Products
CONSUMPTION
Individual, Organization, Secondary Manufacturer, etc.
INPUTS
Land
Water
Structures
Equipment
Materials
Energy
Transport
Technology
Labor
Management
Financing
Information
etc.
$ "Demand" or flow of market signals
"Supply" or product flow

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[a] From NSF study.

Figure 2.—The PMC System Decision Matrix[a]

	Component description	Physically possible	Economically feasible	Institutionally permissable		
Commodity Champions	P 1 Land & water resources					PRODUCTION SUBSYSTEM
	P 2 Production financing					
	P 3 Pest control					
	P 4 Seed availability					
	P 5 Fertilizer needs					
	P 6 Input procurement					
	P 7 Farmers' risk taking					
	P 8 Farm machinery needs					
	P 9 Farm energy requirements					
	P10 Input information					
	P11 Gov't services & regulation					
	P12 Ag research programs					
	P13 Ag information programs					
	P14 Crop organizations					
	P15 Farm labor needs					
	P16 Market info for farmers					
	Ma1 Procurement resources				procurement	MARKETING SUBSYSTEM
	Ma2 Dependable supply					
	Ma3 Procurement financing					
	Ma4 Gov't service & regulation					
	Ma5 Market intelligence					
	Ma6 Transport & storage					
	Mb1 Processing resources				processing	
	Mb2 Processing equipment					
	Mb3 Commodity institutions					
	Mb4 Processing energy					
	Mb5 Processing research					
	Mb6 Processing info programs					
	Mb7 Processing by-products					
	Mb8 Managerial ability					
	Mc1 Distribution resources				distribution	
	Mc2 Distribution financing					
	Mc3 Product market info					
	Mc4 Product transportation					
	Mc5 Market R & D					
	Mc6 Gov't services & regulation					
	C 1 Market penetration					CONSUMPTION SUBSYSTEM
	C 2 Market size					
	C 3 Consumer awareness					
	C 4 Product versatility					

[a] From NSF study.

nomic analysis methodologies for determining feasibility of marketing/consumption components; farm budget analysis can be used effectively at the farm level to determine production feasibility.

Finally, to make effective use of the results of analyses and knowledge base for a particular crop, a formalized strategy for moving into the commercial production stage can be formulated using a technique called critical path programing. An example for kenaf from the NSF study is shown in figure 3.

Some additional observations on economic issues or constraints to new crop introduction are:

1. Lead time and development investments often are long and heavy, and risks are high because of the highly sophisticated nature of much new product development in the chemical, medical, pharmaceutical, and refined proteins areas. A concerted effort is needed to develop an effective partnership between government and the private sector to share in both the risks and the benefits.
2. The degree to which a new crop's development system is vertically integrated affects how well synchronized the establishment of the required subsystem components will be.
3. Many of the products that have been discussed at the workshop are subject to the "lumpy investment" syndrome in which large investments are needed to incorporate changes in production. These crops require much greater knowledge of the economic risks than crops for which investment increments follow a fairly smooth curve.
4. Interest groups and government should join together to form a "New Crops Council."
5. Existing food crops in developing countries are usually produced at no more than 30 to 40 percent of the potential of the land base. Food needs are more likely to be met by improving the ability to grow known crops than by introducing new crops.
6. Products derived from wild stands give commercial value to plants that previously had only local or no value. As demand increases, the cost of the raw product will increase. Once the demand for a product with a limited market and high price is satisfied, the product has near zero value. Production and demand can easily fall out of phase.

Following are the author's comments from an economics perspective on each of the papers presented at the workshop.

An Alternate Use for Tobacco Agriculture: Proteins for Food Plus a Safer Smoking Material

by Samuel Wildman

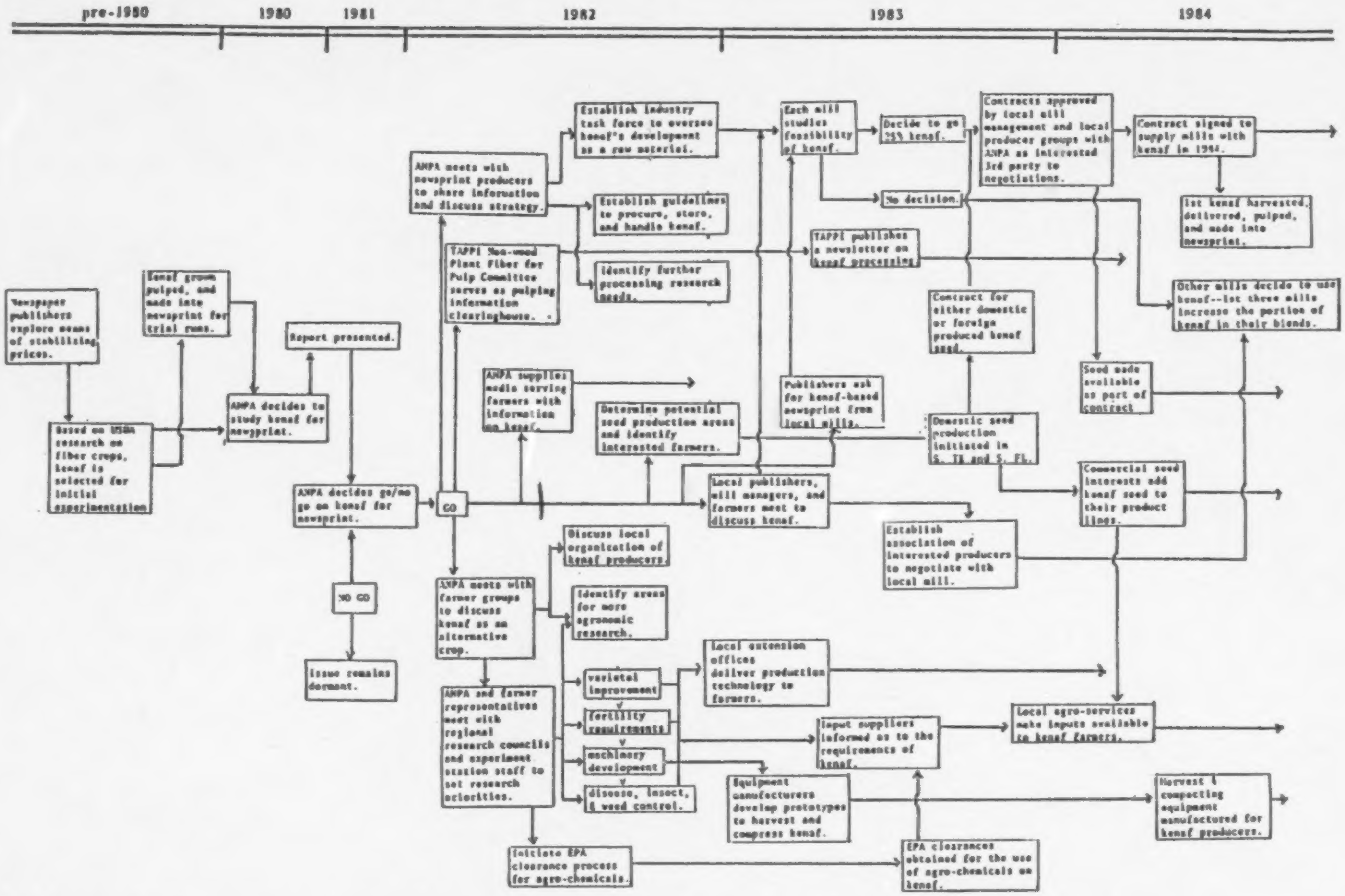
As in the case of many new crop development efforts, this presentation is long on technical process and short on economic feasibility. The shortage of protein in a global sense has to be considered in economic terms if it is to be solved. Demand varies according to the type of protein and whether it is for specialized use, animal use, or general human consumption. With specialized uses and animal use, the product must be able to compete with alternative products in price, availability, and ease of use. With human consumption, it also must compete with other products on the basis of consumer taste preference.

According to Wildman's paper, tobacco protein extracts have two major specialized uses: for specialized diet requirements and as a protein fortifier in the packaged foods industry. Although no information on market size is given, the demand for tobacco protein in specialized diets probably is quite limited. Processing requirements raise serious questions about the economic viability of protein extraction solely for this specialized product. Thus, economic feasibility probably depends on whether the other subproducts can compete in other protein markets.

Protein fortification in the general package foods industry is highly dependent upon final consumer demand. How much more will consumers pay for a protein fortified packaged food? Available evidence suggests that they will pay only marginally more because consumers of packaged foods generally have the purchasing power to get adequate protein from preferred sources, particularly meat. Thus, for this market, price becomes a prime element of economic feasibility. The paper does not provide adequate price information to evaluate the protein's competitiveness in this market, although the information provided suggests that its economic viability is somewhat doubtful. More economic information is needed before the technology's viability can be assessed.

Since the pricing of green sludge and green residue in the animal protein market depends largely on the price structure of the higher value products and the magnitude of the market, their competitive position is speculative. (The green residue would be used mainly for deproteinized cigarette tobac-

Figure 3.—A Crop Introduction Strategy for Kenaf*


pre-1980
1980
1981
1982
1983
1984
Newspaper publishers explore means of stabilizing prices.
Based on USDA research on fiber crops, kenaf is selected for initial experimentation
Kenaf grown pulped, and made into newsprint for trial runs.
ANPA decides to study kenaf for newsprint.
Report presented.
ANPA decides go/no go on kenaf for newsprint.
NO GO
Issue remains dormant.
GO
ANPA meets with newsprint producers to share information and discuss strategy.
TAPPI Non-wood Plant Fiber for Pulp Committee serves as pulping information clearinghouse.
ANPA supplies media serving farmers with information on kenaf.
ANPA meets with farmer groups to discuss kenaf as an alternative crop.
ANPA and farmer representatives meet with regional research councils and experiment station staff to set research priorities.
Initiate EPA clearance process for agro-chemicals.
Establish industry task force to oversee kenaf's development as a raw material.
Establish guidelines to procure, store, and handle kenaf.
Identify further processing research needs.
Determine potential seed production areas and identify interested farmers.
Discuss local organization of kenaf producers.
Identify areas for more agronomic research.
varietal improvement
fertility requirements
machinery development
disease, insect, & weed control.
Local publishers, mill managers, and farmers meet to discuss kenaf.
Local extension offices deliver production technology to farmers.
Equipment manufacturers develop prototypes to harvest and compress kenaf.
Each mill studies feasibility of kenaf.
TAPPI publishes a newsletter on kenaf processing
Publishers ask for kenaf-based newsprint from local mills.
Decide to go 25% kenaf.
No decision.
Contract for either domestic or foreign produced kenaf seed.
Domestic seed production initiated in S. TX and S. FL.
Establish association of interested producers to negotiate with local mill.
Input suppliers informed as to the requirements of kenaf.
EPA clearances obtained for the use of agro-chemicals on kenaf.
Contracts approved by local mill management and local producer groups with ANPA as interested 3rd party to negotiations.
Seed made available as part of contract
Commercial seed interests add kenaf seed to their product lines.
Local agro-services make inputs available to kenaf farmers.
Contract signed to supply mills with kenaf in 1984.
1st kenaf harvested, delivered, pulped, and made into newsprint.
Other mills decide to use kenaf--1st three mills increase the portion of kenaf in their blends.
Harvest & compacting equipment manufactured for kenaf producers.

*(Initiated and coordinated by consumers, i.e., newspaper publishers as represented by the American Newspaper Publishers Association (ANPA).) Goal: To produce 25% of domestic newsprint from pulped kenaf by 1990. From NSF study.

co, so one would assume it would be used as animal feed only when there is surplus.) If only limited amounts of these animal feed byproducts are available, compared with the massive market volume for their established competitors, it is unlikely that the feed industry would be willing to go to the trouble and expense of using minor and/or intermittent amounts of these new products.

In addition to the fortification of packaged foods, the other possible market for human consumption is as a protein supplement for populations that do not have the purchasing power to obtain adequate protein from preferred sources. This probably would have to be part of government programs. The history of attempts to market a protein additive for home prepared foods such as soups and stews as a means of increasing proteins in poor peoples' diets is abysmal.

Poor people on their own often will not buy protein supplements to add to their food, partly because being poor often is coincident with a low level of knowledge and commitment to nutritional needs. Even premixing protein in products bought by poor people has not had significant results. Witness attempts at lysine fortification of rice in Latin America, where housewives often pick out and throw away the slightly off-color lysine rice grain. Attempts in Latin America to encourage low income families to use the protein supplement INCAPARINA so far have been largely unsuccessful. Raising incomes may well be a more viable means of achieving nutritional goals.

In many developing countries, poor people suffer from calorie as well as protein shortages; often the small amount of protein consumed is converted to energy. The first nutritional requirement is to raise energy intake levels; otherwise much of the benefit of increasing protein intake is lost.

The following economic questions need to be answered:

1. In the United States, it is questionable whether the use of tobacco plants for protein extracts will have significant impact on the net income per acre or the expansion of farmers' acreage in tobacco because after the protein has been extracted, tobacco processors would use the residual fibers to fulfill the demand for cigarette production.
2. Investment in commercial processing for tobacco protein is a "lumpy investment." In order to accept the risk of investing in an expensive process change, good knowledge about the economics of the enterprise must be available.
3. The paper presents no economic information about competitiveness of tobacco compared with alternative feedstocks, except to suggest that total biomass per hectare is high compared with many alternative crops. That is not sufficient information to determine tobacco's competitiveness.

A commercial operation may be economically feasible, but the paper has not shown this, even at a prefeasibility level. A serious analysis of the entire PMC system for this crop/product is urgently needed before additional resources are invested in its development.

Leaf Protein Extraction From Tropical Plants

by Lehel Telek

Many of the same economic questions arise with this paper as with Wildman's. This paper also deals almost exclusively with technology and very little with demand, market, costs, and returns, a major weakness in most publicly and some privately funded new crop/product research. Original project design should include resources to do initial and subsequent periodic assessments of economic and institutional factors determining the feasibility of the entire PMC system upon which successful commercial development of the new crop/product depends. The additional cost for such economic/institutional analyses would be marginal, and the savings could be enormous.

Although this paper primarily addresses the animal protein market, human consumption also is contemplated. The comments made on Wildman's paper relating to human consumption are relevant to this paper as well. The LPE process explained in this paper appears to be much more feasible for animal protein production than the extraction process for tobacco. Because the protein extract from the LPE process would be used mainly as animal feed, it probably would be more competitive with alternative sources than with tobacco extracts.

Major weaknesses in the overall concept of processed leaf protein for animals in tropical areas need to be taken into account. There are a number of tropical crops that already are well-established and can be consumed directly by animals, even nonruminants. Although direct consumption may not permit the fine tuning of protein balance needed for optimum feed conversion ratios, this may not be so important in tropical areas as in the U.S. where conversion ratios are critical to profitability. In developing countries where opportunity cost of labor is low and conversion efficiency may be less critical, considerable improvement can be made in animal productivity through direct consumption of many existing, well-established crops. Marginal improvement in productivity of these crops and in their use in animal feeding could be achieved without introducing a processing technique requiring what would be an enormous capital investment in a developing country, as well as specialized knowledge. It seems unlikely that many developing countries will have either the institutional capacity or the economic capacity for large scale processed protein production and use for many years. These countries might be better advised to put scarce resources into improving animal feeding systems based on existing local products for direct consumption before new systems are introduced.

Again, having said this, there probably are areas of the tropical world that are ready for processed leaf protein. Puerto Rico may be one. Nevertheless, there is insufficient information to determine the economic feasibility of the system at present.

The Role of the Alkaloids of *Catharanthus Roseus* . . . .

by Gordon Svoboda

Obviously, marketing alkaloids from the Madagascar periwinkle has been successful. If the divergence between general belief and actual fact about profitability of this cancer drug is as great as Svoboda suggests, some mechanism to counteract misinformation is needed to make venture capital aware of the profit potential of drugs from plants.

Some economic factors incident to this new crop/product area are:

1. The research process to arrive at the point reached for the Madagascar periwinkle is long and high risk. A partnership between government and private industry, where risks of "blind alleys" are shared, could stimulate more activity in the development of pharmaceuticals from plants.
2. Some public/private industrywide mechanism should exist for allocating resources to screening potentially valuable plants, including a standardized system for reviewing crops that merit further research. Resources for research are allocated in a somewhat random and discontinuous way at present.
3. Government regulation of the drug industry, while admittedly in the public interest, has raised the cost of product development and testing until the economic feasibility for many product markets is questionable. Economic efficiencies in the system can be achieved by streamlining compliance with and application of Government regulations, greater use of public resources for product R&D, and earlier attention to economic issues by the product developer.

Chemicals From Arid/Semiarid Land Plants: Whole Plant Use of Milkweeds

by Robert Adams

This paper generally is responsive to the need for applying economic criteria to determine feasibility of new crop introduction. It points out the relative economic advantages of crops with the potential to produce several byproducts of economic value. It also highlights the advantages of looking at crops that do not compete in the same marketplace with domestic crops; some milkweed byproducts compete only with imported products. The paper also attempts to determine comparative advantage of milkweed production in semiarid areas now producing grain sorghum and wheat.

Because there is a lack of knowledge about processing costs for many of the extracts, their farm gate value is speculative and their economic feasibility cannot be predicted yet with any certainty. Nevertheless, the author is to be commended for making this early effort at determining economic feasibility at the production subsector level of the PMC system. Similar efforts, perhaps using the Delphi technique, need to be made for the marketing and consumption subsectors. Efforts at economic data improvement are imperative.

Insecticides, Insect Repellents, and Attractants From Arid/Semiarid Land Plants

by Martin Jacobson

The paper provides intriguing information about seven crops that produce extracts with insecticidal properties. No economic information is provided for any except some yield and price information on neem tree products (oil and cake) in India. Apparently the author recognizes that unless some of the more valuable neem extracts can be efficiently produced and marketed, it is not an attractive income crop for a farmer who probably would earn very little from the harvested seed per tree per year.

Economic screening of the plants described is a necessary next step in determining which of them have economic potential. Applying the PMC systems analysis and using the Delphi technique to improve reliability of the data base could be quite helpful in making these economic choices.

Molluscicidal and Other Economic Potentials of Endod

by Aklilu Lemma

The information provided in this paper reflects the usual bias in new crops research; it emphasizes technological aspects although it recognizes the need for economic analysis.

This paper appropriately points out the potential for developing countries of foreign exchange savings (import substitution) by using domestically produced endod instead of importing chemical molluscicides to control schistosomiasis. Unfortunately, the paper does not provide cost and comparative price data to permit any but the most generalized assessment of economic potential.

A sufficient data base for *Endod* to permit a reasonably reliable PMC System analysis probably exists. Until a detailed analysis is done, the economic potential of *Endod* for the multiple uses proposed will remain largely speculative.

Marine Plants: A Unique and Unexplored Resource

by William Fenical

This paper summarizes some important commercial uses of marine algae for food or food supplements, fertilizer, pharmaceuticals, and in biomedical research. The paper also points out the vast untapped potential of marine plants as sources of biomass, pharmaceuticals, agricultural chemicals, food and food products, and industrial chemical feedstocks. Economic obstacles alluded to include high basic research costs of screening, bioassay, isolation, synthesis, etc.

Implications are that costs and risks of not being able to isolate commercially exploitable products are so great that only with appropriate joint public/private efforts can the potential in pharmaceutical use of marine plants be achieved. For new pharmaceutical uses, present slow progress likely will continue unless the United States makes a public policy decision to increase investments in this type of research.

Strategic and Essential Industrial Materials From Plants—Thesis and Uncertainties

by Howard C. Tankersley and E. Richard Wheaton

This paper presents important preliminary strategic and economic criteria for pursuing national production potential for reducing dependence on foreign imports of a wide array of strategic and essential industrial materials.

In economic terms, the private sector has been unwilling to act on its own initiative, perhaps because it perceives the costs and risks of converting to national production as higher than continuing to import the products. Recent rapid increases in petroleum prices may have altered that outlook for the private sector, but public policy involvement probably is necessary to bring about a significant change of attitude of the private sector. Public policy decisions must relate to underwriting a part of R&D costs and assuring priority of U.S. produced products in the U.S. marketplace. It also may require some innovative arrangements between Government and the private sector concerning initial investments in industrial plant and equipment. Government policy actions for these strategic and essential products clearly are key factors in determining economic feasibility.

Information Gathering and Data Bases That Are Pertinent to the Development of Plant-Derived Drugs

by Norman Farnsworth and William Loub;

and

The USDA Economic Botany Laboratory's Data Base on Minor Economic Plant Species

by James Duke

Both of these data bases are important to furthering production and processing research in the new crops area. However, neither data base focuses on economic data.

Since economic data become outdated more rapidly than production, biological, and processing data, it is more difficult to deal with. However, a central economic data base could be quite helpful in encouraging both public and private sectors to invest in further development of promising new crops and products.

Again, until higher public sector priority is accorded to new crops/products development and reflected through increased R&D funding and appropriate policy actions, it is doubtful that there will be much change in the area of new crops development.

Conclusions

1. For a more coordinated and sustained focus on problems and prospects of new crops/products development, a representative private/public sector group needs to be established at the national level. A "New Crops Council" could: 1) be a clearinghouse for information, 2) provide guidance in establishing priorities, 3) enter into direct R&D, including initial commercial production, for new crops/products with sufficient technological, institutional, and economic promise, and 4) review areas of public policy that inhibit dynamic private involvement in the R&D process, and provide solutions to these.
2. The scientific community itself appears to have some attitudes that tend to dampen private and public sector enthusiasm for developing natural products derived from plants. The bias is toward synthetic organic chemicals and related fields. This reaches into the upper echelons of public and private sector management. If the many apparently sound economic, developmental, and societal arguments for more intense efforts at expanding our useful crops and plants base are valid, a well-coordinated educational process is in order. The public sector should take the initiative in such an educational effort.
3. Past and ongoing efforts at new crops development tend to focus on production and technological process factors, with little or no early attention to economic factors. Although there usually is some general economic rationale for looking at new crops and/or products, that rationale seldom is tested either empirically or with simulated information. A relatively reliable and low cost method for early analysis of economic potential, and identification of elements requiring in-depth economic analysis, was developed in the NSF study referred to earlier. All research projects on new crops should include resources to carry out a PMC Systems analysis at a very early stage, with required periodic updating of information and analysis. The Delphi technique can provide meaningful economic information at a very early stage in research on new crop production, processing, and use.

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